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AN AGENT RELATED TO UGANDA S VIRUS FROM MAN AND MOSQUITOES IN SOUTH AFRICA ‡

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The purpose of this communication is to report the isolation in the Union of South Africa of an agent closely related to Uganda S virus and to present evidence that this agent is pathogenic for man and is arthropod-borne.

After the Tongaland virus expedition of 1955[1] a permanent field station was established in the Ndumu Game Reserve in northern Natal to serve as a base for long-term virus investigations in the coastal lowlands. One aspect of the programme was to search for patients with virus disease in the hope of isolating the aetiologic agents from them. To accomplish this, clinics were held at the field station and at selected kraals within working distance of it, and all persons who presented themselves were attended medically, although only those with fevers were of special interest to our programme. Temperatures were first taken of all present and those having fevers in excess of 100°F by mouth or 101°F *per rectum* were marked with a piece of adhesive tape showing this temperature so that they could be specially examined. Such persons were carefully queried about their illness and examined physically to detect any obvious cause for the fever. If no obvious cause was found a blood specimen was taken and the donor finger-printed. The blood specimen was placed at once in an iced thermos flask and within a few hours the serum was separated and stored on solid CO_2 until it could be transported to the laboratory and thawed for inoculation. These procedures carried out during March 1956 resulted in the isolation of one of the strains discussed in this communication.

The strain of virus isolated from mosquitoes was encountered during the course of work intitiated in an attempt to discover the aetiologic agent of febrile illness which was occurring in the environs of Johannesburg early in 1958. Here again, attempts were made to isolate virus from patients, but these were unsuccessful; the virus strain encountered was obtained from mosquitoes caught in the study area.

Materials and Methods

The materials and methods used in these studies were essentially those which members of this team have used in investigations already reported.[2]

VIRUS ISOLATIONS

Isolation of strain H336. D.M., Native male aged 9 years, was seen at Maponde's Kraal about 1 mile from the Usutu River on 28 March 1956. He was found to have an oral temperature of 100°F. No cause for the temperature was found on physical examination. The child denied feeling ill, but it is noteworthy that the threshold for feeling ill among these Native people is very high indeed; minor ailments are so prevalent that they are commonly ignored and the individual regards himself as sick only if considerably incapacitated or suffering severely. A blood specimen was taken and the child finger-printed. The serum was separated later in the day, frozen and kept on CO_2 until 31 March 1956, when inoculations into infant and adult mice were made in the laboratories in Johannesburg. The infant mice sickened on day 5 and brain passage was successful, resulting in the establishment of an agent which was readily transmissible in either infant or adult mice. A re-inoculation of the original serum specimen into infant and adult mice again resulted in illness and death of the former. Adult mice inoculated with the original serum specimen always remained well, but it should be reiterated that passage material was readily and highly pathogenic in the adult mice. The agent was found to be easily filterable. The designation H336 applied to the strain is the serial number of the blood specimen from which it was isolated.

On 1 May 1956 D.M. was again bled in order to get a convalescent specimen for immunological tests. When the heat-inactivated acute-phase serum and the convalescent specimen were tested against the newly isolated virus, it was found that the convalescent serum neutralized the agent strongly. Finger prints made when the acute and convalescent specimens were taken were compared and pronounced identical.** Thus, the origin of the virus from the patient was proved by both the immunological response of the donor and by re-isolation from the acute-phase serum.

Isolation of virus strain AR1115. Field investigations in the Johannesburg area were undertaken early in 1958 to attempt the identification of agents responsible for pyrexias

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** The willing collaboration of a member of the South African Police, Detective Head Constable P. F. Retief, Local Finger Print Office, Johannesburg, in making this comparison is gratefully acknowledged.

of unknown origin among people residing especially in the environs of Germiston. Attempts were made to isolate virus from the febrile patients and from mosquitoes caught in regions where some of these patients had presumably suffered exposure to mosquito bites. Three strains representing 2 different viral species were isolated from mosquitoes caught along Germiston Lake. Certain features of the catching area at Germiston Lake were closely paralleled in another region a few miles away at Olifantsvlei, and a mosquito catch was made here in the hope of isolating virus. The 34 *Culex* (*Neoculex*) *rubinotus* Theobald taken in the Olifantsvlei catch were designated AR1115 and were inoculated into infant and adult mice. After a 3-day incubation period newborn mice in both litters were either dead or sick. A suspension of the infected brain material was filterable through a Seitz pad and a serially transmissible agent was readily established. The infective agent in the original mosquito suspension caused illness in the adult mice inoculated, but only after a 5–10 day incubation period.

AR1115 virus strain was found to be readily filterable and easily transmissible and, in due course, it was found to be reciprocally, and approximately quantitatively, cross-reactive with strain H336, as will be seen in a later section of this report.

PATHOGENIC PROPERTIES

In mice the H336 isolate causes diffuse vesicular and pyknotic degeneration of nerve cells throughout the brain, most consistently and conspicuously in Ammon's horn, without any resultant leucocytic reaction. Perivascular infiltration in some instances is moderate, but in other instances does not occur. Inclusion bodies have not been found. Lesions have been found only in the central nervous system.

In mice the agent is pathogenic by whatever route it is introduced and the titres by intraperitoneal and intracerebral inoculation are approximately the same—about $10^{-8.5}$.

Ten guinea-pigs inoculated intracerebrally with 100,000 adult-mouse intracerebral LD_{50} showed no significant febrile or other clinical response during the 10 days immediately following inoculation, but showed a good antibody response.

A non-immune monkey, *Cercopithecus aethiops pygerythrus* F. Cuvier, number M805, was inoculated subcutaneously with 6,600,000 LD_{50} of H336 virus. During the 9 days following inoculation the monkey failed to develop elevated temperature. On 7 of the 9 days, tests for circulating virus were made and none was detected when undiluted serum was inoculated intracerebrally into adult mice. The monkey exhibited a good antibody response as a result of the inoculation.

IMMUNOLOGICAL RELATIONSHIPS

Shortly after the H336 strain was isolated it was tested in neutralization tests against antisera for a number of other viruses having comparable incubation periods. None of the sera tested gave significant neutralization. Subsequently all the monotypic antiviral sera on hand were tested against the H336 virus and neutralization of a low order was obtained with Wesselsbron, Zika, dengue 1 and yellow-fever antisera. In a subsequent test the dengue immune serum failed to cross-react, but confirmatory weak cross-reactions were obtained with the Zika, yellow-fever and Wesselsbron antisera. The sera which failed to show neutralization were the following: Semliki Forest, Bunyamwera, Bwamba, West Nile, Pongola, Rift Valley fever, Uganda S, Spondweni, Ilheus, dengue 2, Mengo (EMC), St. Louis, Simbu, Japanese B, Wyeomyia, California, Anopheles A, Anopheles B, Russian SS, louping ill, WEE, EEE, and VEE. The minor cross-reactions with Zika, yellow-fever and Wesselsbron antisera led us to suspect that H336 is a member of Casals' group B viruses. Support was given to this suspicion when it was found that an antigen prepared from the H336 virus was cross-reactive in complement-fixation and haemagglutination-inhibition tests with group B antisera. Similar observations were made in the laboratories of the Rockefeller Foundation in New York.[3] In those laboratories it was also found* that immune serum against Makonde virus,[4] which was found to be a strain of Uganda S virus,[5] gave strong neutralization of the H336 isolate and that an immune serum from Rhesus monkey M4900 immunized with Uganda S virus likewise gave significant neutralization. Tests done in Johannesburg with Makonde antisera, provided through the courtesy of Dr. A. J. Haddow and Dr. M. P. Weinbren, of Entebbe, confirmed that these antisera had strong neutralizing capacity for H336. However, repeated tests with various ampoules of lyophilized serum from the New York laboratories monkey number M4900 failed in our hands to show significant neutralizing capacity.

An apparent relationship having been demonstrated both in the New York and Johannesburg laboratories between H336 and Makonde strains, guinea-pig immune sera were prepared for a special study of the relationships of these agents. Groups of approximately 10 normal guinea-pigs weighing 300–400 g. were bled and the pre-inoculation serum of those in any one group were pooled. The separate groups were then inoculated with either Uganda S or H336 viruses in relatively small dosage. After an appropriate period the animals were bled and cross-neutralization tests were done with the antisera. Guinea-pigs of groups 17 (Uganda S) and 19 (H336) were exsanguinated at the only post-inoculation bleeding. Animals of groups 54 (H336) and 56 (Uganda S) were, however, each bled on 2 separate occasions and the quantitative differences in antibody content of the sera were determined. Included in the tests were pre- and post-inoculation sera of monkey M805 and rehydrated serum of M4900 immunized in New York with Uganda S virus. Two tests were done with these reagents. In the first, the sera were tested in the usual way without dilution or addition of any accessory substances. In the second test, 0·1 ml. quantities of fresh normal monkey serum were added to equal quantities of test sera, and to these mixtures 0·2 ml. quantities of virus were added. In both tests the mixtures were incubated for 1 hour at 37°C and tested by intracerebral inoculation into young adult mice. Results of the tests are shown in Table I, from which it is clear that there is a close relationship between Uganda S and H336 viruses. There is also evidence that the two are not identical, in that M4900 serum, although it neutralized the homologous virus did not neutralize H336 virus, and in the fact that some of the cross-reactions are not quantitative. As example of the latter it may be seen that, in the tests made without added serum, the two Uganda S guinea-pig antiserum pools neutralized 50 times as much of the homologous virus as of H336.

A vaccination-and-challenge experiment was done to study the relationship of H336 and Uganda S viruses. Uganda S virus is much less pathogenic by peripheral inoculation

* Dr. Max Theiler, personal communication.

TABLE I. RESULTS OF CROSS-NEUTRALIZATION TESTS WITH UGANDA S AND H336 VIRUSES AND THEIR RESPECTIVE ANTISERA

	H336 virus				*Uganda S virus*			
	Nothing added		*Fresh serum added*		*Nothing added*		*Fresh serum added*	
Serum	*Titre*	*Logs neut.*	*Titre*	*Logs neut.*	*Titre*	*Logs neut.*	*Titre*	*Logs neut.*
M 805 pre-inoc.	8·2		7·5					
M 805 post H 336	4·5*	3·7	5·15*	2·35				
M 228 normal					5·6		6·0	
M 4900 post Uganda S † ..			7·4	0·1			3·64	2·36
M 4900 post Uganda S ‡ ..			7·25	0·25			3·48	2·52
GP 17 pre-inoc.	7·5		8·12		6·0		5·36	
GP 17 post Uganda S ..	6·53	0·97	6·36	1·76	3·3	2·7	2·84	2·52
GP 56 pre-inoc.	8·0		7·6		5·33		5·46	
GP 56 post Uganda S 8 days	7·4	0·6	6·62	0·98	3·48	1·85	4·0	1·46
GP 56 post Uganda 30 days	6·4	1·6	5·25	2·35	2·0	3·33	3·33	2·13
GP 19 pre-inoc.	7·36		7·75		5·52		5·6	
GP 19 post H 336	5·14	2·22	4·64	3·11	4·12	1·4	3·4	2·2
GP 54 pre-inoc.	7·25		7·5		6·29		5·87	
GP 54 post H 336 8 days ..	5·5	1·75	6·0	1·5	3·75	2·54	3·4	2·47
GP 54 post H 336 29 days ..	4·5	2·75	4·0	3·5	3·4	2·89	2·5	3·37

* Tests done with different bleedings taken 38 days apart. † Added fresh serum was heat-inactivated.
‡ Added fresh serum was unheated.

than H336. The immunization of mice was attempted by the intraperitoneal injection of 0·5 ml. quantities of virus reconstituted to 0·5% from lyophilized Uganda S infected mouse brain stock. There was a good deal of mortality following the inoculation of the living virus. However, extra mice had been vaccinated and enough remained for the challenge inoculations. 21 days after the injection of living virus as vaccine, vaccinated mice and unvaccinated mice of the same age, which had been reserved for this purpose, were challenged by intracerebral inoculation of serial decimal dilutions of Uganda S or H336 virus. Results of the tests were as follows:

Titre Uganda S in normal mice	7·0
Titre Uganda S in vaccinated mice	4·58
Titre H336 in normal mice	8·0
Titre H336 in vaccinated mice	6·5

The immunity induced by the Uganda S vaccine was thus approximately ten-fold as effective against the homologous virus as against H336.

Another approach to the study of the relationship of Uganda S and H336 viruses was made by testing the same human survey sera against both agents. 280 sera were tested against the two viruses by identical methods. The results of these tests are shown in Table II, from which it may be seen that, although there is agreement in the results in 76% of cases, there was, nevertheless, disagreement in 10%. Critical analysis of the tests showing the discordant results indicates that this was not due to differences in virus dosage, for the 30 sera which were protective against H336 virus and negative against Uganda S virus, were actually tested against virus dosages averaging 421 and 212 LD_{50} respectively.

TABLE II. RESULTS OF PROTECTION TESTS WITH H336 AND UGANDA S VIRUSES AGAINST THE SAME HUMAN SERA

Virus		*H336*			*Total*
		Protective	*Inconclusive*	*Negative*	
Uganda S	Protective	24	2	0	26
	Inconclusive	26	2	2	30
	Negative	30*	4	190	224
	Total	80	8	192	280

* Mean virus dosage: H336, 421 LD_{50}. Uganda S, 212 LD_{50}.

For comparison with the afore-mentioned results a study was also made to determine the correlation between results of routine protection tests with H336 and the mosquito strain AR1115. 120 human sera were tested against both these agents by identical methods, and in this instance there was complete agreement in 91·67% and disagreement in only one of the 120 sera tested, as shown in Table III. This result, together with HAI and cross-neutralization tests which showed quantitative neutralization of AR1115 virus by H336 antisera, led to the conclusion that the H336 and AR1115 strains are identical with each other, and related to but not identical with Uganda S virus. The latter relationship is, however, closer than the relationship of most group B viruses to each other and there is doubt whether the differences observed justify the application of a separate specific name for the South African isolates.

TABLE III. RESULTS OF PROTECTION TESTS WITH H336 AND AR1115 STRAINS AGAINST THE SAME HUMAN SERA

Virus strain		*H336*			*Total*
		Protective	*Inconclusive*	*Negative*	
AR 1115	Protective	29	1	0	30
	Inconclusive	6	1	1	8
	Negative	1	0	81	82
	Total	36	2	82	120

TRANSMISSION OF H336 STRAIN BY *Culex* (*Culex*) *univittatus* THEO.

This mosquito—already known from the work of Taylor *et al.*[6] to be a vector of West Nile virus—is one of the dominant mosquitoes in the coastal lowlands of Natal. It was decided to test its potential as a vector of certain agents isolated there. Female adults reared from eggs collected from wild-caught gravid females were used in the test. Since little was then known concerning the viraemia produced by H336 virus in any laboratory animal and because difficulty was often experienced in getting *Culex univittatus* to bite mice, the mosquitoes were exposed to infection by allowing them to take a meal consisting of infected mouse brain, defibrinated rabbit blood and sterile glucose solution. The infective feed was administered in a piece of glass tubing. The mosquito was first caught up in the tube, its exit being barred by a cotton pledget at the centre of the tube and another at one end. Virus was introduced onto the absorbent pledget in the centre of the tube from the open end opposite to that in which the mosquito was confined and soon soaked through to become available to the mosquito. The mosquito could be manipulated to a certain extent by moving the cotton pledgets. When each mosquito had engorged, it was released into a cage and then transferred for maintenance to a 3×1 inch glass vial containing at the bottom a wad of damp paper. The vial was closed by gauze held in place by adhesive tape and was stored in a humid atmosphere. The tubes in which the mosquitoes were exposed to the infective material were sterilized by boiling. An aliquot of the virus used to infect the mosquitoes was titrated and an endpoint of $10^{-8 \cdot 5}$ was obtained. Fourteen *Culex univittatus* took the infective feed.

Attempts to transmit by bite were made by manually restraining baby mice over the gauze covering the tubes in which the individual mosquitoes were kept. Much difficulty was experienced in inducing the mosquitoes to feed, but visible blood was taken by separate arthropods on days 6, 7, 8, 9, 13 and 14. All these bitings apparently resulted in transmission, for the bitten mice sickened and those not sacrificed died. Specificity tests were done on the first 3 and these were all positive, showing conclusively that the cause of illness in the mice was H336 virus.

DISCUSSION

Regardless of the fact that the youth from whom the H336 strain was isolated disclaimed feeling ill, it is obvious that the agent obtained from his blood is pathogenic for man. Unfortunately the patient was seen only once during his illness and did not then exhibit any specific symptoms. It is probable that the illness he suffered was of very mild nature and it may be that this is a characteristic of infection with this agent. The fact that considerable numbers of human sera from residents of the Tonga lowlands[7] and various localities in Mozambique[8] exhibit neutralizing antibodies for H336 virus indicates that it not uncommonly attacks man.

The isolation of an apparently identical strain of virus from mosquitoes is tentative evidence of the fact that the agent is arthropod-borne. Conclusive proof of this fact is the successful transmission of the agent by *Culex univittatus* in laboratory experiments. Whether *Culex rubinotus*, from which the virus was isolated, is a vector is not proved by these results, but in view of the fact that *Culex univittatus*, a known vector of a related virus, can be shown capable of transmitting H336, it seems likely that a natural vector relationship exists.

SUMMARY

1. A virus was isolated from the blood of a Native child during an access of fever. Comparison of acute and convalescent sera from the virus donor showed the development of specific neutralizing antibodies during convalescence and indicated the aetiologic relationship of the virus to the febrile episode.

2. A strain of virus apparently identical with the aforementioned strain was isolated from *Culex rubinotus* mosquitoes caught at Olifantsvlei, near Johannesburg.

3. These two strains, apparently identical with each other, are closely related to but apparently not identical with Uganda S virus. The relationship is closer than that between most viruses of Casals' group B (to which the new agents belong) and for this reason a separate specific name is not to be applied at this stage.

4. The new agent has been successfully transmitted in the laboratory by the bite of *Culex univittatus* mosquitoes, and is therefore capable of being arthropod-borne.

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VAN DIE REDAKSIE : EDITORIAL

TABLETTE VIR DIE BEHANDELING VAN DIABETES

Tolbutamied (rastinon, artosin) word tans baie in hierdie land gebruik vir die behandeling van diabetes. Dit het die gebruik van die oorspronklike karbutamied feitlik heeltemal vervang. Karbutamied was sterker maar ook meer giftig. Daar is geen afdoende bewys dat tolbutamied ooit agranulositose veroorsaak het nie; trouens, dit het skynbaar soms net ligte tydelike leukopenie veroorsaak. Ligte huidsuitslag kom voor, maar dit is gewoonlik nie nodig om die toediening van die middel hieroor te staak nie. Sommige pasiënte hou nie van die middel nie om vae redes—hoofpyn, naarheid, en so meer; maar hierdie klagtes kom gewoonlik nie meer voor as wat sou gebeur het indien 'n troosmiddel in plaas van tolbutamied gebruik is nie.

Dr. Lawrence[1] vertel die ongewone storie van 'n effens gesette man van 62 wat 19 jaar lank ligte diabetes gehad het. Hy het tolbutamied, 1·5 g. daagliks, 'n paar weke lank geneem met 'n goeie uitwerking op sy bloedsuiker, toe hy 'n vergrote lewer, 'n ernstige graad van gestippelde edeem van die bene, en askites ontwikkel het. Daar was nie geelsug nie. Die toediening van tolbutamied is gestaak en na 'n week van rus in die bed en die gebruik van asetazolamied het die pasiënt ten volle herstel. Dit is glad nie duidelik dat die skade deur die betrokke middel veroorsaak is nie, en selfs as dit die geval was, sou dit 'n unieke geval uit tienduisende wees. By proefdiere is lewerskade nie deur tolbutamied veroorsaak nie, alhoewel sommige van die verwante antidiabetiese samestellings (bv. chlorpropamied) bepaald 'n giftige uitwerking op die lewer gehad het, veral by honde. Die verslag van hierdie enkele geval hoef ons dus nie te verhoed om tolbutamied te gebruik nie.

Die uitwerking van hierdie sulfonamied-verwante middels is nog onbekend, maar prakties kan dit as geldig aanvaar word dat hulle die produksie van insulien stimuleer of dat hulle die uitwerking van die endogene insulien wat wel voortegebring word, versterk. Hulle kan insulien *nie* vervang nie en dit lyk nie of hulle die uitwerking van insulien wat ingespuit word, versterk nie. Die middels is waardeloos vir die soort diabetes wat by jong persone voorkom—daardie pasiënte wat onderhewig is aan ketose; trouens die gebruik van sulke middels by hierdie soort geval is definitief nie aangewese nie. Oor die algemeen het die sulfonamied-verwante middels geen waarde as hulle saam met insulien gebruik word nie; hulle help ook nie om moeilik beheerbare diabetes in bedwang te hou nie. Selfs in die ouer soort pasiënt is die waarde van dié middels twyfelagtig. As die diabetes van 'n pasiënt goed onder beheer gehou kan word deur sowel insulien as tolbutamied, is dit waarskynlik dat die toestand net so goed beheer sou kon word as enigeen van hierdie middels alleen gebruik word. Een van hierdie middels is dus eintlik onaktief.

Dit is teleurstellend dat 'n toenemende aantal pasiënte wat aan die begin goed met tolbutamied beheer is, weer 'n styging van bloedsuiker toon na maande of jare van behandeling. Hierdie ‚sekondêre mislukking' van tolbutamied is 'n werklike verskynsel en nie noodwendig verwant aan enige onreëlmatigheid van die dieet of toename van die pasiënt se gewig nie. Die redes hiervoor is nie voor die hand liggend nie. Daar skyn geen bewys te wees van skade aan die pankreas, en dus verergering van die diabetes nie. Byvoorbeeld, die hoeveelheid insulien benodig na die mislukking van tolbutamied is meer as wat dit voor die tyd was; ook het Gepts[2] op grond van outopsiestudies gevind dat die histologiese toestand van die pankreas na behandeling met karbutamied of tolbutamied geensins swakker is as die pankreas van soortgelyke pasiënte wat net met insulien of dieet behandel is nie. Trouens, by een of twee sulke pasiënte het dit hom opgeval dat hulle pankreasse selfs tekens toon van regenerasie van aktiewe korrelagtige betaselle. Regenerasie word nie gewoonlik by hierdie soort pasiënt aangetref nie, en dit kan dus 'n aanduiding wees dat die betrokke middels die neiging toon om 'n abnormale pankreas te laat herstel. Daar is egter geen kliniese bewys van die verligting van die basiese diabetiese toestand deur die gebruik van tolbutamied nie. Die middel kan by geleentheid weerhou word sonder dat die beheer van die pasiënt se diabetiese toestand verswak; dit gebeur egter ook in die geval van insulien en mag maar slegs wisselinge in die verloop van die siekte weerspieël.

Tot dusver is daar geen bewys dat diabetiese pasiënte wat met tolbutamied behandel word meer of minder onderhewig is aan die sogenaamde bloedvat-‚komplikasies' van die siekte nie. Tolbutamied het geen uitwerking op die cholesterol in die serum nie.

Chlorpropamied (diabinese) het 'n sterk chemiese ooreenkoms met tolbutamied en dit werk skynbaar op dieselfde manier, maar dit is sterker. Dit kan 'n ernstige graad van hipoglisemie veroorsaak en moet nie in groter dosisse as 500 mg. gebruik word nie. Die uitwerking van die middel is langer, sodat genoeg daarvan vir die hele dag in een dosis gegee kan word. Behalwe ligte newe-uitwerkings kan die middel skynbaar afwykings van lewerfunksietoetse toon en selfs geelsug van die soort wat gevind is met die gebruik van largactil. Dit is dus nie 'n middel wat onoordeelkundig gebruik moet word nie en, soos tolbutamied, kan dit slegs gebruik word vir pasiënte wat nie onderhewig is aan ketose nie. Dit het die voordeel dat dit die bloedsuiker verlaag by sommige diabetiese pasiënte waar tolbutamied nie geslaag het nie.

Die samestelling bekend as DBI (fenetielbiguanied) is chemies onverwant aan hierdie middels en verlaag die bloedsuiker deur anerobiese glikolise te verhoog. Dit is effektief in sommige pasiënte met ernstige diabetes, wat ook geneig is tot ketose, maar dit veroorsaak onhoudbare gastro-intestinale irritasie in baie gevalle. Die plek van hierdie middel by die behandeling van diabetes is twyfelagtig, maar die verwagting is dat dit 'n sekere waarde kan hê by die behandeling van moeilik-beheerbare pasiënte wat maklik in koma verval.

Op die oomblik skyn dit redelik te wees om die gebruik van tolbutamied te probeer in gevalle van die ouer soort diabetiese pasiënt wat nie ketose gehad het nie en in wie se geval dieetmaatreëls alleen nie genoeg is om die glisemie te beheer nie. Voordat besluit word om hierdie middel vir 'n onbepaalde tyd te gebruik, moet dit duidelik wees dat dit effektief is, en daar moet gelet word op die moontlikheid van sekondêre mislukkinge. Chlorpropamied kan gebruik word in plaas van insulien indien tolbutamied nie slaag nie, maar die geneesheer moet bewus wees van die moontlike giftige gevolge.

1. Lawrence, R. D. (1959): Brit. Med. J., I, 644.
2. Gepts, W. (1957): *Contribution à l'Étude Morphologique des Ilots de Langerhans au Cours du Diabète.* Les editions ‚Acta Medica Belgica'.

SECOND THOUGHTS ON TABLETS FOR DIABETES

Tolbutamide (rastinon, artosin) is at present widely used in this country in the treatment of diabetes. It has virtually supplanted the original carbutamide, which, although somewhat more powerful, was distinctly more toxic. It is not definitely established that tolbutamide has ever caused agranulocytosis; in fact it only very rarely appears to produce a mild and temporary leucopenia. Minor skin rashes do occur, but do not usually necessitate the withdrawal of the drug. Some patients complain of 'not liking the new tablets' for vague reasons—headache, nausea and so on, but it is quite probable that such complaints are no more frequent than would be found if a placebo had been used in place of the tolbutamide.

An unusual story has been told by Dr. Lawrence,[1] concerning a moderately obese man of 62 who had had mild diabetes for 19 years. He had been receiving tolbutamide in a dosage of 1·5 g. daily for some weeks, with good effect on his blood sugar, when he developed an enlarged liver, with gross pitting oedema of the legs and ascites. He was not jaundiced. The tolbutamide administration was stopped, and after a week's bed rest and some acetazolamide the patient had fully recovered. The evidence here is by no means conclusive that the damage was caused by the drug—even if it were so it appears to be a unique case out of many tens of thousands. In experimental animals, liver damage has not been produced by tolbutamide, although some of the related antidiabetic compounds (e.g. chlorpropamide) have proved definitely toxic to the liver, specifically in dogs. In any event, this single case report should not deter one from the use of tolbutamide in general.

The mode of action of these sulphonamide derivatives is still uncertain, but from a practical point of view it may be taken as a working hypothesis that they act by stimulating the production of insulin or enhancing the effect of whatever endogenous insulin is being produced. They are *not* able to replace insulin in any way and do not appear to enhance the effect of injected insulin. They are quite valueless in the young variety of diabetes—in those patients who are subject to ketosis—in fact their employment in this type of person is definitely contra-indicated. In general they are of no value when used in addition to insulin—they do not help to control the 'brittle' case, and even in the older type of patient the value of the mixture is very doubtful. If a patient is well controlled on both insulin and tolbutamide, it is most likely that he (or she) would be equally well controlled on one or other used alone—in other words one of the two drugs is a sleeping partner.

It is disappointing that an increasing number of patients who are satisfactorily controlled on tolbutamide at first again show a rise in blood sugar after months or even years of treatment. This 'secondary failure' of tolbutamide is a real phenomenon, and not necessarily related to any dietary laxity or increase in the patients' weight. The reason for it is not obvious. There appears to be no evidence that the pancreas becomes damaged, so worsening the diabetes. For one thing, after a tolbutamide failure, insulin requirement is no more than it had been previously and, secondly, Gepts,[2] by means of autopsy studies, has found that the histological state of the pancreas after carbutamide or tolbutamide therapy appears in no way worse than the pancreas of similar patients who had been treated with insulin or diet only. In fact he observed a remarkable feature in one or two of such patients—namely that their pancreases actually showed evidence of regeneration of active, granular beta cells. Regeneration is not normally seen in this type of patient, and might be taken as suggesting that the drugs concerned actually tend to produce repair of the abnormal pancreas. There is, however, no clinical evidence of amelioration of the basic diabetic condition by tolbutamide. Occasionally the drug may be discontinued without worsening of the patient's diabetic control, but this may also be seen with insulin and perhaps merely reflects fluctuations in the course of the disease.

There is so far no evidence to indicate any change in the liability to the vascular 'complications' of diabetes in patients who are being treated with tolbutamide. It has no effect on the serum cholesterol.

Chlorpropamide (diabinese) is chemically very similar to tolbutamide, and apparently acts in the same way, but is more powerful. It is capable of producing severe hypoglycaemia, and should not be used in doses larger than 500 mg. per day. Its effect is much longer lasting, so that the day's requirement can be given in one dose. Apart from mild side-effects it can apparently cause abnormalities in liver-function tests and even jaundice, probably resembling that associated with largactil. It is not, therefore, a compound to be used indiscriminately and, like tolbutamide, it can only be used in those patients who are not liable to ketosis. Its advantage is that it may be effective in lowering the blood sugar in some diabetics in whom tolbutamide has failed.

The compound known as DBI (phenethylbiguanide) is chemically unrelated and reduces blood sugar by enhancing anaerobic glycolysis. It is effective in some severely diabetic, ketosis-prone patients, but produces intolerable gastro-intestinal irritation in a very high proportion of subjects. Its place in the treatment of diabetes is uncertain, but it might be hoped that it will have some value in rendering more easily controlled the extremely brittle patient who wanders so readily in and out of one or other sort of coma.

At the present time it would appear reasonable to try tolbutamide in the older type of diabetic who has not had ketosis, and in whom dietary measures alone are insufficient to control the glycaemia. It must have become clear that this drug is effective before it is indefinitely continued, and watch must be kept for secondary failures. Chlorpropamide, instead of insulin, may be tried if tolbutamide fails, but the physician must be aware of its possible toxic effects.

1. Lawrence, R. D. (1959): Brit. Med. J., **1**, 644.
2. Gepts, W. (1957): *Contribution à l'Étude Morphologique des Ilots de Langerhans au Cours de Diabète.* Les editions 'Acta Medica Belgica'.

URTICARIA: AN AETIOLOGICAL PROBLEM AND THERAPEUTIC CHALLENGE*

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Urticaria is a condition in which swellings appear more or less suddenly on the skin of the trunk and limbs in the form of raised, circumscribed, oedematous, white wheals with a surrounding area of erythema. In giant urticaria large surfaces of the body are simultaneously involved. There is much discomfort to the patient from the accompanying irritation or itching that occurs. In acute urticaria the swellings last some hours or may persist for two or three days, fresh wheals appearing as the others fade. The whole episode of an acute attack may be over in a few days or in a week or two.

Bouts of acute urticaria may recur at intervals of months or years and after a few such experiences the patient is usually able to attribute these attacks to some food he has eaten (shellfish, nuts, eggs, fruit, etc.), some drug he has taken or been injected with (aspirin, penicillin, etc.), insect bites or stings, exposure to cold, light or local pressure, or to plants, animals or substances he has handled. The patient may have learned that the 'itchy bumps' tend to appear during times of strong emotional stress of a particular type. In women an attack may occur premenstrually or during some other stage of the menstrual cycle.

Such attacks of urticaria occurring occasionally in this way may be manifestations of an allergic reaction, but it is obvious from the above that they are not necessarily so.

Chronic urticaria persists for weeks or months or even years with or without periods of remission. The aetiological diagnosis may be difficult and sometimes defies exhaustive clinical and laboratory investigations.

Angioneurotic oedema (Quincke's oedema) is aetiologically and pathologically a similar condition except that the reaction-site is more deeply placed and involves the arterioles in the subcutaneous tissues. Localized, large diffuse swellings appear in the looser connective tissues, mainly affecting the periorbital regions, lips, tongue, throat and genitalia, although any part of the body may be thus affected. These swellings tend to recur in the same sites in subsequent attacks and there is hardly any associated itching, although much discomfort is present and the swellings, if on the lips, eyes and face, occasion alarm by the unsightly distortion of the features that may result. The condition becomes of serious import when the glottis is affected, for the oedema there interferes with swallowing and breathing, and in sudden attacks asphyxia may ensue if the patient is not promptly attended to.

Acute urticaria and angioneurotic oedema may occur separately but the local swellings of the latter often appear together with the whealing of urticaria. Steinhardt[1] reported that angioneurotic oedema occurred in 216 of 500 patients with urticaria. He thought that the proportion was becoming greater, probably on account of the increasing therapeutic use of penicillin, because both conditions usually occur together in penicillin reactions.

Very often dermographism can be demonstrated in persons with the urticaria tendency, by the wheal that follows the direction of stroking of the skin with the finger nail.

PATHOLOGY

The urticarial wheal is characterized by local exudation of fluid into the upper papillary layer of the cutis, producing oedema from dilatation of blood vessels and increased permeability of their walls. There is, in addition, a mild perivascular cellular infiltration. The urticaria lesion is reminiscent of Sir Thomas Lewis's 'triple response' in anaphylaxis, due to histamine-dilatation of the capillaries and venules, increased capillary permeability, and arteriolar dilatation from an axon reflex producing the flare or erythematous area. The itching in urticaria is probably associated with the involvement of the nerve endings near the surface of the skin.

As there is no essential difference aetiologically and pathologically between urticaria and angioneurotic oedema except for the site of reactions in the patient's skin, the term 'urticaria' will be used in the rest of this paper to include both conditions.

INCIDENCE

Urticaria generally occurs in young and middle-aged adults. It is difficult to estimate the incidence because the condition is, of course, not notifiable and patients are mainly seen in private practice. Swinney[2] found a 26% incidence of urticaria in over 1,000 patients, and Sheldon *et al.*[3] reported that 15·7% of 1,424 college students had experienced at least one attack.

In the Union of South Africa urticaria is a not uncommon condition in Europeans and there is no reason to believe that the incidence or causative factors involved are different from those in urticaria elsewhere. As part of a study now in progress of allergy in the non-European population of South Africa the question of urticaria in the African (Bantu), Eurafrican and Indian is being investigated. In the meanwhile preliminary enquiries have established the fact that urticaria is uncommon in the Bantu people of the Witwatersrand. Through the courtesy of the Medical Superintendent it was ascertained that at the Baragwanath Non-European Hospital in Johannesburg, with an annual admission rate of nearly 20,000 men, women and children, only 8 cases of severe urticaria were admitted in 1958. In the out-patient department of that hospital only one or two cases a week are

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seen in a daily attendance of 1,000-2,000 persons. Among the medically-selected male Natives of the 20-40 year age-group employed as underground and surface labourers on the gold mines of Johannesburg and the Reef urticaria hardly ever occurs. Mine medical officers whose views were sought reported that only one or two cases of acute urticaria are seen a month in their individual mine Native labour populations of up to 25,000 men. Chronic urticaria is virtually unknown. It is in this connection worth recording that, in contrast to the frequency in Europeans, penicillin reactions are relatively uncommon in the Bantu.

IS URTICARIA AN ALLERGIC DISORDER?

All too often urticaria is regarded as an unequivocal allergic disorder and the approach to it is based on this conception. As a result a frequent request is for skin tests to determine the cause and the appropriate desensitization vaccine. The matter is not as simple as that. Urticaria is not necessarily an allergic disorder. It is not often that skin testing is of value, because it does not follow that positive skin reactions necessarily represent the aetiological agents and, of course, desensitization procedures under the circumstances would have no value. Stokes *et al.*[4] in their study of 100 patients found that the exclusion of substances and foods to which the patient gave a positive scratch-test skin reaction was conspicuously unsuccessful as a therapeutic measure. Blood eosinophilia is not characteristic of urticaria, and if present may merely reflect an accompanying parasitic infestation.

An allergic condition, strictly speaking, results from an antigen-antibody reaction with the liberation of histamine or histamine-like substances which provoke the well-known allergic manifestations of hay fever, asthma, eczema etc. Summer hay fever is an example of an antigen-antibody reaction where a specific grass pollen produces nasal congestion, rhinorrhoea and sneezing in a grass-pollen sensitized person. Similarly, an attack of asthma following contact with a cat by a cat-sensitive person is another example of the same mechanism.

In the same way as not all asthma is allergic in origin so also does urticaria not always have an allergic basis. Indeed, from the *aetiological* standpoint there is essentially no difference between urticaria and asthma. In regard to asthma Brocklehurst[5] described 'SRS-A'—a slow-reacting substance which plays a part in anaphylaxis—and suggested that it was of particular importance in human asthma, where antihistamine drugs have proved to be relatively ineffective. This provides a further indication that the search for the aetiology in urticaria should not be confined to the histamine effect of an allergic reaction.

While acute urticaria is sometimes of allergic origin, chronic urticaria most commonly is not. Indeed, true allergic chronic urticaria probably hardly accounts for one-third of cases seen. Chronic urticaria may, of course, in certain instances obviously be an allergic manifestation as, for example, in an egg-sensitive person who persists with a diet containing egg. Nevertheless, it is seldom that true exogenous allergens are found in patients who seek advice about chronic urticaria. Such a sufferer has probably long since discovered the responsible agent and has avoided or eliminated it; or he presents himself with an allergic respiratory condition or for gastro-intestinal disturbances with urticaria as an accompanying manifestation.

Swineford[6] found only 35% of cases of urticaria to be allergic in character, with the aetiological atopic agents represented by pollens, dusts, foods, drugs and insect bites and stings, as well as therapeutic serums, insulin and liver. Siegel and Bergeron[7] reported that in 111 of their cases only 18% had a history of other allergies and 28% came from allergic families, although Swinney[2] thought that a history of urticaria was 2½ more times commoner in persons who have had asthma or hay fever. According to Mitchell *et al.*[8] 88% of patients with chronic urticaria had eosinophil counts of 5% or less.

HISTAMINE AND HISTAMINE-RELEASING AGENTS IN URTICARIA

There seems little doubt that the whealing in urticaria and the diffuser swellings in angioneurotic oedema result from the action of histamine on the vascular tissues of the skin. Whilst there are numerous substances that can act in the same way, histamine according to Herxheimer and Schachter[9] is the most prominent whealing agent in man. Experimentally, the injection of histamine intracutaneously or its introduction into the tissues by iontophoresis produces whealing effects.

In the allergic forms of urticaria the antigen may reach the dermis from the alimentary tract from drugs or foods, with a liberation of histamine when contact of the antigen is made with a specific antibody in the skin. There is some suggestive experimental evidence[10] that the antigen-antibody reactions there do not release histamine directly but by way of an enzyme, possibly a tissue protease.

On the other hand histamine production in some persons may result from the products of tissue metabolism; thus, the ingestion of certain foods may be associated with histamine production directly without the intervention of the antigen-antibody mechanism of allergy. Paton,[11] for example, showed that decoctions of alcohol-extracted muscle of the lobster, crayfish and mussel when injected into the cat's isolated perfused skin released histamine; and this probably explained the well-known effect of over-indulgence in crustacean delicacies. He also indicated[12] other agents capable of releasing histamine in addition to sensitizing substances of the allergic antigen-antibody reaction, viz: venoms, toxins and other traumatizing agents, proteolytic enzymes like trypsin; surface-acting agents—Tween 80 and bile salts; and also egg white, dextran, horse serum, and many drugs, including morphine, codeine and atropine. It has been found that stings from certain insects or contact with some plants directly introduce into the skin a complex solution of histamine, acetylcholine and serotonin. Schachter[13] stated that bee and wasp venom released histamine and also that extract of strawberries possessed marked histamine-releasing activity.

West[14] showed that mast cells are exceptionally rich in histamine and that in many instances the total histamine content of an organ could be accounted for in this way. He pictured the action *in vivo* of the basic histamine liberators as accumulating in mast cells in consequence of their affinity for heparin, the heparin complex increasing the permeability of the mast-cell granules from which the free histamine diffused out.

Johnson[10] showed that there were marked variations in histamine levels in various regions of the human skin, the highest levels being on the upper lip and eyelid. Weiser[15] found in addition that mast cells were abundant in the tongue, uterus, thymus and bladder, as well as around large and

small blood vessels and in the subserous and submucous layers of the digestive tract.

Inderbitzin and Dobric,[16] however, in their recently published experimental investigations in white rats on histamine in skin anaphylaxis, made some interesting and possibly significant findings. They were forced to the unexpected doubt whether the histamine released in cutaneous anaphylaxis was in a form in which it could act on blood vessels. Although the cutaneous oedema provoked by chemical histamine releasers could be strongly influenced by antihistaminic compounds, the oedema of the local antigen-antibody reaction could not. This observation seems to support the idea that the histamine released by the one mechanism is in some way different from the other.

Steinhardt[1] and others have pointed out that histamine release was not sufficient to explain adequately all cases of urticaria, which also could be due to the release of acetylcholine in the skin as the result of cholinergic nerve-fibre stimulation, a mechanism probably responsible for the urticaria associated with heat, emotion and exercise.

Serotonin (5-hydroxytryptamine) is another substance which is concerned with the reaction of the skin to injury and for the subsequent development of oedema. West and Parratt[17] stated that, like histamine, serotonin was probably stored in the skin of some species and that the two amines together might account for most of the vascular changes seen in injury. Herxheimer and Schachter,[9] however, considered it very unlikely that the release of serotonin, although it increased capillary permeability in the rat skin, was of significance in urticaria or angioneurotic oedema of man.

DIAGNOSIS: (A) CLINICAL

The diagnosis of urticaria is relatively simple, especially in the acute form, when the wheals appear suddenly, leaving hardly any sign on fading. There is no subsequent peeling as in toxic conditions, nor is there usually any fever or other constitutional signs. However, in some patients there may be a simultaneous occurrence of colic and diarrhoea suggesting a foodstuff as the common cause of both skin and gastro-intestinal conditions.

Papular urticaria was described by Tate[18] more than 20 years ago as being essentially different from true urticaria, on the basis of the presence of both conditions simultaneously in one patient, where the urticaria, consisting of evanescent wheals, was due to fish. Cornbleet[19] agreed with this view, arguing that, whilst pruritus was common to both conditions, papular urticaria unlike urticaria was not improved by antihistamine therapy. Blank *et al.*[20] studied the role of insects in the aetiology and urged the use of DDT in its control. Rook and Frain-Bell[21] summarized the present outlook on the condition in their declaration that most if not all papular urticaria was the result of acquired sensitivity to the bites of insects, particularly bugs and fleas. The correctness of this view has been amply confirmed since that time.

Urticaria pigmentosa, a disease of unknown aetiology, showing pigmented skin macules and nodules, is associated with the accumulation of mast cells in the dermis.

DIAGNOSIS: (B) AETIOLOGICAL

Drugs, foods, infections, contactants, physical agents and psychological stresses must at present be regarded as the principal factors responsible for the precipitation of urticaria in susceptible persons. Different workers have at various times emphasized the special significance of one or other of these factors. There are additional causes of urticaria no less important in individual cases but operating much less frequently, and there is also a substantial residue of cases where the aetiology remains unknown.

Kahn and Grothaus,[22] on the basis of the successful therapeutic outcome in 17 out of 18 cases of chronic urticaria, were of the opinion that foods were almost exclusively responsible. Siegel and Bergeron, in their series of 115 cases of urticaria and angioneurotic oedema, concluded that by far the largest single cause was penicillin by injection—24%, in a general drug incidence rate of 32%. Foods accounted for 12%, infections for 10%, and in about 33% of the cases the aetiology was not determined. Steinhardt[1] stated that 30% of their cases of urticaria were caused by foodstuffs and, of these, 17% recovered when the incriminated food was removed from the diet; drugs accounted for 17% of cases; infective agents for 14%; contactants for 14·5% and physical causes for 3·3%. Psychogenic factors were not mentioned. In Swineford's series[6] of urticaria patients 35% were regarded as of allergic origin; infections and parasitic infestations accounted for 27%; 15% had a psychological basis; 6% were of physical origin; 5% were due to hormonal factors; while the aetiology in 12% of the cases remained unexplained.

To guide enquiry into the patient's general and clinical history and to facilitate the aetiological diagnosis in urticaria, the classification of the possible factors in Table I may prove of assistance. The classification is not made on an 'allergic' or 'non-allergic' basis because some of the agents listed may in certain circumstances act as true allergens whilst in others they promote the release of histamine or histamine-like substances by a mechanism other than the antigen-antibody reaction. It should be borne in mind, too, that the endogenous factors may be significant either primarily or in association with exogenous agents. The following comments enlarge upon certain of the aetiological factors in Table I:

TABLE I. URTICARIA AND ANGIONEUROTIC OEDEMA
POSSIBLE AETIOLOGICAL FACTORS

Exogenous		*Endogenous*
Inhalants		*Physical*
Pollens		Cold
Dusts (industrial, textile, etc.)		Heat
		Light
		Pressure
		Exercise
Ingestants		*Infective*
Foods		Bacterial
Drugs (including antibiotics and biological products)		Parasitic
		Fungal
Injectants		*Endocrine*
Drugs		Menstruation
Serum		Menopause, etc.
Insect bites and stings (venoms)		
Contactants		*Psychological*
Plants	Metals	Resentment
Animals	Drugs	Frustration
Woods	Chemicals	Hostility
Textiles	Dyes	Fear
Plastics	Cosmetics etc.	Anger etc.

Association with other diseases

Inhalants

Inhalant substances, particularly pollens and various dusts (textiles, silk) have occasionally been reported as causing urticaria. Waldbott and Merkle[23] described 26 cases of urticaria due to the inhalation of pollen; in 12 of these the skin lesion was confined to the pollen season but in 14 the condition was protracted by what appeared to be secondary factors.

The diagnosis of inhalant sensitivity may be confirmed by skin testing with extracts of the suspected materials. Desensitization with their extracts may be necessary if avoidance is not possible.

Ingestants

Foods. Any food may be responsible for an attack of urticaria in a person specifically sensitive to such foods. Particularly important are sea-foods (lobster, crab), fruits, nuts, milk, wheat and chocolate. It is interesting in regard to sea-foods that Drake[24] found mussels especially common in provoking the condition, with oysters as an infrequent offender. Skin testing for food sensitivity may be tried and will sometimes provide useful information. Positive skin reactions, however, do not necessarily imply clinical sensitivity nor do negative reactions exclude the possibility. Trial diets or food elimination tests provide the best means of discovering the responsible foodstuffs, but these techniques require patience as well as full cooperation from the patient. Desensitization with food extracts is not satisfactory and should not be employed. From a practical point of view it is not of great significance whether a specific food idiosyncrasy is based upon a true allergic mechanism or whether some foods act otherwise as histamine liberators. Whatever the underlying mechanism they must be removed from the patient's diet.

Drugs. Drugs which produce urticaria by ingestion are generally known to the patient or are suspected during the course of careful history-taking. They should of course be avoided. Skin testing is not indicated nor is desensitization of value. The possibility should be remembered of skin and other reactions resulting from the ingestion of penicillin in milk from cows treated with this drug for mastitis. Zimmermann[25] reported that in 1957 in the USA 11% of milk samples were contaminated with measurable amounts of penicillin. He found support for the diagnosis of penicillin sensitivity in such cases in the clearing of the urticaria in 4-7 days by the use of penicillinase.

Injectants

Insect bites and stings. Urticarial wheals may occur in sensitive persons as a result of mosquito bites and bee and wasp stings. The reactions with mosquito and bee venom appear to be a true allergic phenomenon because the patient does not manifest clinical reactions in the early onslaughts by these insects but becomes sensitized to their injections subsequently. Winkelmann,[26] however, reported that bee and snake venoms could release histamine *per se* without the presence of specific antibody. Less is known about wasp stings, which in some people possibly produce the same sensitization phenomenon. On the other hand, wasp kinin is an effective whealing agent to man on intradermal injection.[9] West and Parratt[17] found that there was a high concentration of serotonin in wasp venom, probably accounting for some of the features of the human skin reactions following wasp stings.

Serum. Serum reactions resulting from the injection of antitetanus or other therapeutic sera may include urticaria.

Drugs. Urticaria often follows the injection of drugs, which may act as true allergens or through the liberation of histamine by some other mechanism. The allergic drug reaction is seen after penicillin administration in a person who has been sensitized by previous administration of this antibiotic. Penicillin injections are today probably the commonest cause of urticarial whealing, which usually, along with other symptoms, appear within 24 hours or a week or two after the penicillin but persists for weeks or even months thereafter. The possibility of such delayed reaction should be borne in mind when deciding whether penicillin or similar drugs could have been the cause of the urticaria. Other drugs incriminated in the causation of urticaria include more especially aspirin, pyramidon, quinine, barbiturates, and various metal salts.

Contactants

Plants. Dermatitis and occasionally urticaria result in some persons from direct contact with certain plants. In the USA poison ivy (*Rhus spp.*) is the most important offender in this respect. The term 'nettlerash' sometimes used for urticaria is significant; the skin lesion does not appear to represent an allergic reaction. According to West and Parratt,[17] there are in the nettle the histamine releasers serotonin and acetylcholine, in addition to histamine itself.

Animals. Whealing occurs in some persons on handling cats, dogs or other animals.

Drugs. Urticaria may occur from direct contact with drugs, more especially the antibiotics and local anaesthetics.

Textiles. Silk, nylons and other materials have been reported as giving rise to contact dermatitis with whealing.

Diagnosis in contact dermatitis is relatively simple because enquiry into the history of the case will usually reveal the responsible agents. If thought necessary, confirmation may be obtained by the patch test.

Physical Factors

Skin lesions associated with physical factors have generally been referred to as manifestations of 'physical allergy', but in the strict sense they are not allergic conditions at all. Nevertheless there is sometimes evidence of allergic association in a family history of allergy, the occurrence of eosinophilia and mainly, as in Rajka and Asboth's 4 cases,[27] a positive passive-transfer reaction. On the other hand, it seemed to Swineford[6] that the reactions in 'physical allergy' were mediated by mechanisms other than those of anaphylaxis; support for this view was given by the persistence of the lesions, the obvious roles of friction and temperature changes and the failure of antihistamines and sympathomimetic drugs to provide relief.

Cold. Some workers have attributed the skin reactions from cold to a defect in the heat-regulating mechanism. Goldberg and Pittman[28] thought that the aetiology of cold sensitivity could not be clearly defined and the most one could say was that the skin manifestations were due to increased reactivity of the normal response of the peripheral vascular system. Wolf[29] suggested that the effect of cold was that dermatolytic antibodies combined with the skin cells at a low temperature.

Heat, exertion, trauma. Morgan[30] stated that heat, and exertion which produces heat, could rise to cholinergic urticaria; and that this is probably induced by the liberation of acetylcholine through the parasympathetic nervous system with a secondary release of histamine.

Light. Wolf[29] suggested that light altered the tissue-protein constituents of the skin, rendering them antigenic, and Ehrlich[31] agreed that light urticaria was an allergic rather than a photo-dynamic phenomenon on the fact that passive-transfer reactions were positive although all agents failed to relieve the patient. Partington[32] also found that the reaction in man due to ultraviolet light was not influenced by antihistamines. Epstein,[33] in an interesting study, referred to work on the mechanism of solar urticaria, differentiating that due to visible light, where the passive-transfer test was negative, and that caused by ultraviolet light, where this test was positive and the condition helped by antihistamine therapy. Claesson *et al.*[34] thought that the active substances in the action of ultraviolet light on the skin could not be clearly defined nor could the participation of histamine or histamine-like substances be confirmed. From their experimental investigations they concluded that the mediator substance in the skin was 5-hydroxytryptamine or some similar agent.

Infection

The question of the existence of true bacterial allergy is a controversial one. While positive tuberculin, mallein, lepromin and similar skin reactions, as well as the association of streptococcus products with rheumatic fever, indicate sensitivity to the corresponding microorganisms, it is not so easy to establish scientifically that the bacteria of the respiratory or gastro-intestinal tract are in fact responsible for the usual allergic manifestations which characterize hay fever, vasomotor rhinitis, asthma, eczema, etc. There is thus reason for the doubt that bacterial sensitization is responsible for urticaria, although the possibility of the production of histamine or histamine-like substances by their metabolic activities under certain circumstances cannot be overlooked.

Dutton,[35] some 12 years ago, concluded from his studies of chronic urticaria that low-grade chronic infection was the commonest aetiological factor. There is, however, little agreement with this view. Kahn and Grothaus[22] did not find the correction of infected foci of value. Similarly Siegel and Bergeron,[7] in their study of 115 cases of urticaria and angioneurotic oedema in children and young adults, did not observe a cause-and-effect relationship on removal of infections or infestations; and Mitchell *et al.*[8] also felt that focal infection was not significant. In our experience, whilst we always recommend search for and elimination of foci of infection, we have not often found laboratory evidence of such infections in persons with chronic urticaria.

Infestation with animal parasites has been reported in aetiological association with urticaria—especially the intestinal worms (ascaris, oxyuris, tapeworm); amoebiasis and hydatid disease have also been held responsible. Cohen and Criep[36] referred to previous reports of urticaria occurring with malaria and infestation with roundworms and flatworms, and described their own findings of chronic urticaria of undetermined aetiology in 28 patients where 19 had an associated amoebiasis. Thomas and Rideout[37] also quoted evidence of urticaria accompanying malarial paroxysms and disappearing after the administration of antimalarial drugs. They described a patient with vivax malaria where the initial paroxysm was accompanied by giant urticaria and oedema of the glottis, which reappeared in the second paroxysm.

The finding of blood leucocytosis would be helpful in confirming a state of infection, and eosinophilia if present would lead to the suspicion of the presence of animal parasites.

Psychological

There is considerable difference of opinion about the part played by emotional factors in skin lesions, including urticaria, but there is little doubt of this association, even if not in a primary role.

Graham, Wolf and Wolff[38] showed that changes in tissue sensitivity occurred with varying life situations and emotions. They demonstrated that the arterioles and minute vessels of the skin exhibited dramatic changes in function during experimentally-induced alteration in feeling states. Certain persons during periods of resentment in reaction to symbols of assault exhibited dilatation of arterioles followed by transudation of fluid resulting in oedema of the skin. Further, under these circumstances the skin exhibited increased sensitivity to a host of foods, pollens, drugs and simpler chemical agents. Kaywin,[39] in the study of emotional factors in urticaria, concluded that the onset of attacks was precipitated by a particularly frustrating experience in a shy, withdrawn, easily-embarrassed, passive, dependent and immature person. Graham[40] stated that dramatic life situations responsible for attacks were almost exclusively those in which the patient developed resentment when he saw himself a victim of unjust treatment about which he could do nothing.

Urticaria Associated with Other Diseases

Winkelmann[26] drew attention to the occurrence of chronic urticaria in association with certain systemic diseases including mastocytosis (urticaria pigmentosa), carcinoma, lymphoma, liver disease, rheumatoid states, and obstructive jaundice. In addition, transient urticaria is sometimes found in myelogenous leukaemia where the blood histamine level is high. Wolf[29] referred to its occurrence also in Loeffler's syndrome, periarteritis nodosa and Hodgkin's disease.

TREATMENT

In the treatment of the acute urticaria attack, antihistamine therapy is used successfully except perhaps in that due to penicillin. Loveless and Dworin,[41] as well as Steinhardt,[1] reported control in about 80% of cases. It is wise to persevere with antihistamine administration for a week or two after the urticaria has disappeared. Parker[42] found that in 20 cases not responsive to antihistamine alone the patients benefited by combined calcium-antithistamine therapy.

Adrenaline or ephedrine is indicated in acute forms of urticaria, and ACTH or corticosteroids may be essential in severe forms of angioneurotic oedema.

Complaint by the patient of accompanying gastro-intestinal discomfort may be revealing, because nausea, vomiting, colic and diarrhoea may be further evidence of a food idiosyncrasy. Foodstuffs considered aetiologically responsible should of course be avoided by the patient.

A thorough physical examination is essential in each case of urticaria, more especially to find any underlying disorders and to determine the presence of foci of infection serving to keep alive urticarial manifestations. In this connection especial attention should be paid to dental, nasopharyngeal, gastro-intestinal, gall-bladder, prostatic, cervical and other infections.

As has been shown above, infection as an aetiological agent in urticaria is not accepted by everybody. Nevertheless

there is a possibility that during an infected state the tolerance to histamine produced by allergic or other mechanisms may be lowered. Laboratory aid should be invoked in the search for animal parasites or unusual bacteria, and in the examination of the blood for eosinophilia and leucocytosis.

Close attention should be given to the question of drugs in the aetiology. The patient should be questioned about the recent therapeutic administration of penicillin or other antibiotics. It should be remembered that urticaria may appear as a late sequel perhaps weeks after penicillin has been given. As the patient may not be acquainted with drugs medically administered he should be asked about recent illnesses or operations where medicaments of some kind might have been given. It is wise to refer to 'medicines' rather than to 'drugs' in this connection because in the latter expression he would not be likely to include laxatives, sedatives, headache powders, sleeping tablets, tranquillizers, nerve or health tonics, and similar household remedies.

In the control of chronic urticaria it is important not to be obsessed with the idea that the condition is of necessity an allergic disorder. An indication will usually be obtained from a detailed history of the patient whether there is an allergic basis or whether endogenous physical, infective, endocrine or pyschological factors are predominant. A family history of allergy or a personal history of asthma, hay fever, sinusitis or atopic eczema may confirm a suspicion of an allergic origin in a particular case. Further careful questioning, supported by skin testing if necessary, will suggest inhalant factors or foodstuffs responsible for the condition. If so, these should be avoided if possible or specific desensitization against the inhalant sensitivities should be carried out.

In chronic urticaria histamine desensitization is generally not of much value, although it has been found of benefit in urticaria due to penicillin and it should be tried in the so-called physical allergy where urticarial wheals are associated with pressure, heat, cold, light or friction.

Saline purgatives may be required both to reduce fluid in the tissues and to remove irritating foreign substances from the gastro-intestinal tract.

Walzer,[44] in his studies of the experimental wheal, demonstrated that it was induced faster when alcohol was ingested with or before the specific whealing food. This may be an indication for the patient to avoid alcohol, with its vasodilating effects, as well as stimulating foods.

Vitamin K by mouth was recommended by Black,[43] who found a diminished level of prothrombin, sometimes notably so, in 65% of 156 chronic urticaria patients studied. There was relief in 60% of the cases, particularly in those patients showing a prolonged coagulation time.

The possibility of overt penicillin ingested in milk or other dairy products should be borne in mind.

If, after thorough investigation, allergic, infective or other causal agents cannot be detected, consideration should be given to the possibility that stress factors are responsible for the skin manifestations.

The therapeutic approach to the psychogenic basis of physical disorders is, of course, a study in itself. As a rule there is no need for specialized psychotherapeutic measures. Encouragement of the patient to talk of his condition will generally reveal to the experienced physician a broad picture of his emotional state and an attempt should be made in the course of further sessions to assess its nature and significance. This type of interview conducted with patience and understanding will in itself benefit the patient, and every effort should be made in the course of these talks to give him an understanding of the fact that both physical and emotional stresses may be productive of the same type of bodily reaction. It must be remembered, however, that the stress state itself need not be the sole cause of the skin trouble. It may well be that under such circumstances urticaria may result from drugs or infections, as well as from allergens which would probably be tolerated without symptoms under normal conditions.

SUMMARY

The clinical and pathological aspects of urticaria and angioneurotic oedema are described.

Attention is drawn to the relatively low incidence of urticaria in the African (Bantu) population.

The aetiology of urticaria is discussed as an allergic disorder associated with the release of histamine or histamine-like substances in the characteristic antigen-antibody reaction of allergy and as a manifestation of their release by other mechanisms.

A classification of the possible causative factors of acute and chronic urticaria and angioneurotic oedema is given and explanatory comments made on some of the more important *exogenous agents* (inhalants, ingestants and contactants) and *endogenous factors* (physical, infective and psychological) involved.

The treatment of the acute attack and the approach to the control of chronic urticaria are suggested.

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KERATOSIS FOLLICULARIS SERPIGINOSA (LUTZ)

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Keratosis follicularis serpiginosa is 'n seldsame huidsiekte wat deur Lutz in 1952 beskryf is. Tot dusver is oor ongeveer 35 gevalle in die wêreldliteratuur verslag gedoen. In Suid-Afrika is 2 gevalle deur Marshall en Lurie[1,2] beskryf, en Marshall (mondelinge mededeling) het nog 2 ander gevalle, albei in blonde seuns wat ongeveer 9 jaar oud is, gesien. Die seuns het die afwykings ongeveer 4 jaar lank gehad. By een geval het daar, behalwe aan die nek, ook nog letsels voor die ore, op die ken, en tussen die wenkbroue voorgekom. By die ander geval het die afwykings op die elmboë en dye voorgekom. Op een plek waar 'n letsel verdwyn het, het klein papeltjies oorgebly wat by histologiese ondersoek tipiese miliêre siste was. Die volgende geval is deur die skrywers waargeneem, en 'n addendum oor nog 'n geval word bygevoeg:

Geval 1

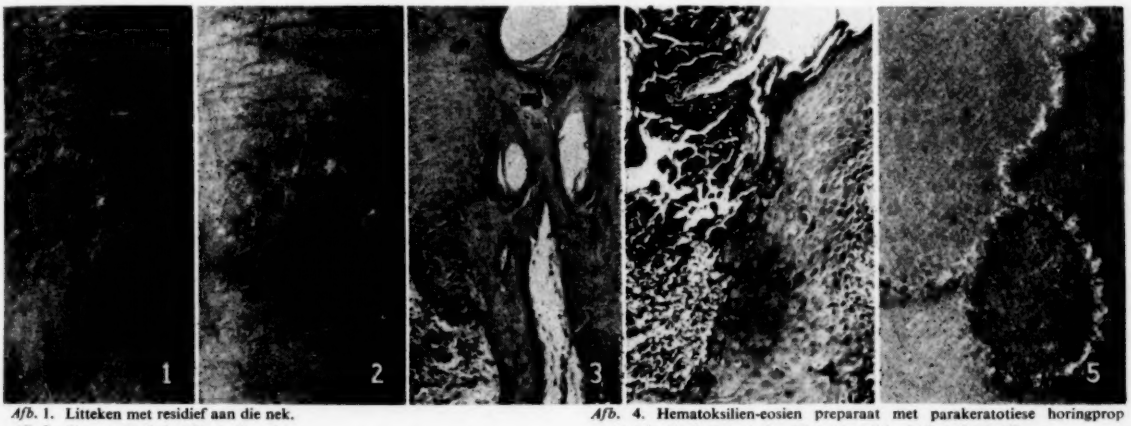
'n Gesonde blonde seun van 12 jaar is in September 1957 die eerste keer gesien. Hy het toe gekla oor 'n sogenoemde omloop op sy nek wat reeds 4 maande aanwesig was en nieteenstaande behandeling uitgebrei het.

By ondersoek is die volgende gevind: Aan die linkerkant van die nek was 2 aaneensluitende halfmaanvormige serpigineuse sirkels met retikulêre sentrale atrofie. Die rante het bestaan uit vratagtige papels (Afb. 2). Die papels wat vasgesit het, het geringe bloeding getoon by verwydering. Aan die regterkant was ook geringe retikulêre degenerasie (soos by 'n verouderde huid) sigbaar, egter sonder papels rondom hierdie area. Enkele verspreide papels het verder aan die nek voorgekom. Die halfmaanvormige letsel aan die nek is totaal uitgesny en die geïsoleerde papels met CO_2-sneeu behandel.

Twee maande later was daar 'n hipertrofiese litteken met verskillende nuwe papels rondom die litteken te sien (Afb. 1). Verder het nuwe papels aan die linker-elmboog en -knie voorgekom. Die letsels wat met CO_2-sneeu behandel is, het heeltemal genees sonder littekenvorming. Een van hierdie nuwe papels is per stansbiopsie verwyder en op Sabouraud-agar gekweek. Daar was geen groei nie. 'n Vars papel van die elmboog en die oorspronklike letsel is histologies ondersoek en deur Woerdeman en Scott[3] saam met nog 'n geval uit die dermatologiese kliniek van prof. dr. J. R. Prakken, te Amsterdam, beskryf.

Histologies word die volgende afwykings gevind: Hiperkeratose en akantose van die epidermis met follikulêre proppe. Die proppe bestaan uit verskillende lae van keratotiese, parakeratotiese en afgebreekte materiaal. Die onderste derde deel, wat direk tot in die dermis deurdring, kleur donkerblou met hematoksilien-eosien kleurstof en vertoon ook 'n sterk elastien kleuring. Waar dit in die dermis deurdring, is daar 'n ontstekingsreaksie met fibroblaste, limfosiete en vreemde-voorwerp reusselle. Die stratum retikulare en stratum papillare vertoon versterkte elastien kleuring met verdikte en gefragmenteerde vesels. Haarfollikels word ook aangetas.

Die siekte kom meer by manlike persone voor, en dit is ook beskryf saam met kongenitale afwykings soos die sindroom van Ehlers-Danlos en mongoloïde idiotisme.[4,5] 'n Oorsig van 6 Suid-Afrikaanse gevalle van keratosis follicularis serpiginosa (Lutz) word in Tabel I aangegee.



Afb. 1. Litteken met residief aan die nek.
Afb. 2. Gegroepeerde letsel aan die nek.
Afb. 3. Hematoksilien-eosien preparaat met dermale letsel bestaande uit gedegenereerde kollageen en sellulêre infiltrasie.
Afb. 4. Hematoksilien-eosien preparaat met parakeratotiese horingprop wat tot in die dermis strek. (Geval van Marshall en Lurie.[1,2])
Afb. 5. Ringvormige letsels met sentrale atrofie in 'n pasiënt met mongoloïde idiotisme.

BESPREKING

Miescher[6] is van mening dat die primêre afwyking uit hipertrofiese en hiperplastiese elastiese vesels (elastoma) bestaan wat deur die epidermis afgestoot word met hiperkeratose, parakeratose, en akantose. Hierdie mening word egter deur ander skrywers bestry.[1-4,7]

Marshall en Lurie[1] het 'n definitiewe verband met haarfollikels aangetoon. Hulle het ook aangetoon hoe 'n lanugohaar deur die follikel die dermis binnedring.

Die juiste geaardheid van hierdie sonderlinge siekte is nog nie met sekerheid vasgestel nie. Enkele ondersoekers meen dat die bewering van Miescher wat betref die patogenese juis is.[8,9] Die moontlikheid van elastoïde degenerasie van kollageen moet egter sterk oorweeg word.

Haber[4] vind dat die hipertrofiese elastiese vesels van die papillêre laag eerder regeneratiewe vesels is en die einde, en nie die begin nie, van die reaksie aandui nie. Hy wys ook

TABEL I. SUID-AFRIKAANSE GEVALLE VAN KERATOSIS FOLLICULARIS SERPIGINOSA (LUTZ)

Skrywer	*Geslag*	*Leeftyd*	*Huidskleur*	*Lokalisasie*	*Ander Afwykings*	*Duur*
1. Marshall en Lurie	M	9 jaar	Blond	Nek	Geen	4 jaar
2. Marshall en Lurie	M	11 jaar	Blond	Nek	Geen	1½ jaar
3. Marshall	M	9 jaar	Blond	Nek, wenkbroue, ken, elmboë, knieë.	Geen	4 jaar
4. Marshall	M	9 jaar	Blond	Nek, elmboë, knieë	Geen	4 jaar
5. Scott en Gordon	M	12 jaar	Blond	Nek, elmboë, knieë	Geen	4 maande
6. Scott en Gordon	M	12 jaar	Blond	Nek, ore, gesig, arm	Mongoloïde idiotisme	6 maande

op die moontlike betekenis van sweetbuise in die proses. Dit is waarskynlik dat talgkliere ook kan meedoen.[3]

Miescher[6] het die moontlikheid van 'n verband met die siekte van Kyrle (hyperkeratosis follicularis et parafollicularis in cutem penetrans) geopper. Hy het hiervoor egter min steun van andere gekry. Histologies bestaan daar dan ook geen enkele grond vir hierdie bewering nie.

In 'n onlangse publikasie beskryf Hitch en sy medewerkers[8] die eerste 5 Amerikaanse gevalle. Een geval het by 'n Kleurling voorgekom. Hulle stel voor om, soos Dammert en Putkonen, die naam ‚elastosis perforans serpiginosa' te gebruik. Daar bestaan egter nog soveel verskil van mening oor die patogenese van die siekte en, tot tyd en wyl dat die saak beter opgeklaar is, lyk dit wenslik om die oorspronklike benaming van Lutz te bly behou.

Daar is min bekend oor die prognose van hierdie siekte. Tot dusver het meeste gevalle by jong persone, om en by die puberteit, voorgekom. Dit is waarskynlik 'n goedaardige selfterminerende siekte. Dit is merkwaardig dat al die Suid-Afrikaanse gevalle by persone met 'n blonde huidskleur voorgekom het.

Wat behandeling betref het hoë dosisse vitamien A skynbaar 'n gunstige uitwerking. Deur vernietiging van die letsels met CO_2-sneeu of die elektrokouter kan genesing soms verkry word.

OPSOMMING

'n Beskrywing word gegee van 'n derde Suid-Afrikaanse geval van keratosis follicularis serpiginosa (Lutz) sowel as 'n oorsig van die ander wat waargeneem is.

Ons wens dr. E. M. v. Zinderen Bakker van die Universiteit van die Oranje-Vrystaat hartlik te bedank vir die maak van die eerste mikrofoto en drs. J. Marshall en H. I. Lurie vir die mikrofoto van hulle geval.

ADDENDUM

Sedert hierdie artikel geskryf is het ons nog die volgende geval waargeneem:

'n Blonde Blanke seun van 12 jaar wat aan mongoloïde idiotisme ly, het sedert 6 maande letsels aan sy nek ontwikkel. Die vermoede was dat dit omlope was.

By ondersoek is aan albei kante van die nek halfmaanvormige letsels bestaande uit serpigineuse areas van horingpapels gevind. Die sentrale gedeeltes het duidelike atrofie vertoon (Afb. 5). Verder was daar enkele papels aan sy gesig, ore en regter-arm aanwesig. Histologiese ondersoek het die tipiese beeld van keratosis follicularis serpiginosa vertoon.

Dit is dus nog 'n geval van hierdie seldsame aandoening by 'n mongoloïde idioot.[3-5]

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DOES ROAD SAFETY CONCERN MEDICINE?

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The object of this article is, firstly, to discuss how far road safety is a matter of concern for the medical profession and, secondly, to suggest ways and means to ensure that applicants for drivers' licences are, in fact, fit and proper persons to drive vehicles as potentially dangerous as the ordinary motor car and the heavier motor vehicles.

THE MALADY

How does Road Safety concern Medicine?

Analysing road safety we find that it concerns 3 types of fitness: (1) Road fitness, which is the concern of engineers and road-builders; (2) vehicle fitness, which is the concern of manufacturers and motor garages, and (3) human fitness, which is the concern of the medical profession. In fact, this is why the profession exists.

In endeavouring to deal with the subject of road safety from the medical angle, we cannot exclude non-medical factors such as suggestions for the promotion of road safety which, even if they are non-medical in appearance, are essentially medical matters in the sphere of public health. For it is the doctor who is called in first in a medico-legal capacity to see if the driver is sober and fit to drive, and it is the doctor who is called upon to give first aid to the injured on the spot or in the casualty wards or hospital theatre. Road accidents and road safety concern life and death, wounds, maiming, first aid, surgery, medicines, physiotherapy, and rehabilitation.

For factory and mine accidents and for infectious diseases, there are special public health regulations, but there are none for road safety. We cannot rely on safety belts, blood donors and surgical teams to minimize the occurrence of road accidents; preventive measures must be taken. Certain diseases affecting driving ability should therefore be made notifiable, as in other notifiable diseases affecting the public health. Road safety is a matter of public health and it is time that this was recognized. It is just as important as town planning, ventilation and sewerage which are directly connected with medicine and public health and are the subjects of legislation. Road accidents are the greatest killer and maimer and speed is an important cause of accidents. With proper preventive measures these accidents would be largely avoidable and could perhaps be reduced by as much as 85% in the first year of trial.

Is Existing Legislation Sufficient?

Section 41 (1) (*f*), (*g*) and (*h*) of the Cape Road Traffic Ordinance (1955) lays down which persons, from the medical angle, are disqualified from obtaining or holding a learner's or driver's licence, namely: Those who are addicted to narcotic drugs or intoxicating liquor, or are suffering from epilepsy, sudden attacks of giddiness or fainting, bad vision (standard is given), mental disorder or defect, or 'from any other disease or physical disability which is, or will be likely, to render him incapable of effectively driving and controlling a motor vehicle . . . without endangering public safety'.

Regarding a person's competency to drive a motor vehicle, 3 aspects present themselves, viz. (1) The moral aspect: Is the applicant's character such that he will drive in a responsible way with due regard to the rules of the road and the rights and safety of others? (2) The question of physical and mental fitness: Is the applicant's health and condition such as to allow him effectively to drive and control a motor vehicle? (3) The question of driving ability: Is the applicant a competent driver? Can he properly handle the vehicle? The third question is the concern of the officers appointed to examine candidate drivers.

As a profession, we are concerned with two aspects of road safety, namely, the examination of individuals with regard to their physical and mental fitness for driving, and the cleaning-up process after accidents. But, in view of our primary aim as a profession—the maintenance of public health—we ought to have an interest in the prevention of accidents. We are really concerned, therefore, not only with the state of health of the individual but with his moral calibre.

As regards a candidate's character, unless he is well known to the doctor who is examining him, the doctor would hardly be in a position to say anything about his character, and it is not suggested here that he should do so. But the medical profession, through its Association, could urge legislation ensuring that an applicant must show the Issuer of Licences at least 2 testimonials from reliable sources, as well as a police report about his criminal record.

A brief examination of the application forms for learners' and drivers' licences will show how inadequate they are. The applicant for a learner's licence is himself expected to answer whether he is unfit or disqualified from driving, or a drug or alcohol addict, an epileptic or mentally disordered or defective. Naturally most people would answer in the negative, and a person of questionable character would certainly not say he was unfit or disqualified. The attention of the medical practitioner is then drawn to the answers given by the applicant and he is asked to declare that he has examined the applicant and that in his opinion the applicant is not disqualified in terms of the relevant sections of the Ordinance, from obtaining a learner's or driver's licence. The medical certificate required in the application for a driver's licence is equally vague. No degree of fitness is laid down for the guidance of the doctor. The law does not state what conditions or diseases or combinations of diseases render a person unfit to drive. The matter is left to the discretion of the individual doctor.

If a doctor decides that an applicant is not fit to drive a vehicle, there is no place on the form for him to state his finding. He can only refuse to put his signature to it and there is nothing to prevent the applicant from going from doctor to doctor until he finds one who is prepared to fill in the form.

It is therefore suggested that the forms should be redesigned to enable doctors to state positive findings concerning age, state of health, diseases and the like. The form should also make provision for the doctor to state whether in his opinion, the applicant is a fit and proper person to drive, despite the presence or absence of disease or physical defect. In fact, the form should give the doctor *carte blanche* to say what he feels is relevant and proper.

It is also suggested that the medical certificate should be printed on a detachable form and that the doctor should be required to send it direct to the Issuer of Licences and not to hand it back to the applicant. Furthermore, if the doctor desires another opinion, the case should be referable to a panel of doctors—at the request of the applicant himself or at the doctor's request.

What Degree of Health is Necessary to Driving Fitness?

The contra-indications for driving are numerous when it comes to physical illness, but it is only when these diseases are severe that they should be considered as disabling. There are many diseases which may gradually render a person unfit for driving, for example, diabetes and rheumatoid arthritis in their more aggravated forms. The following diseases are of special importance in this respect:

(*a*) Diseases of the central nervous system, especially those affecting the higher centres.

(*b*) Diseases of the locomotor system, especially when the effects are incapacitating, as in paralysis, rigidity, paraesthesia and amputation.

(*c*) Diseases which affect the senses of vision, hearing, balance, and touch and pain.

Mental and cerebral diseases are far more serious than physical diseases or disabilities. Symptomatic diseases are dangerous unless made unsymptomatic by drugs, but where diseases remain symptomatic, despite treatment, or where treatment produces symptoms, the conditions are equally dangerous. Hypertensive episodes are as bad as hypotensive faints produced by therapeutic agents. Insulin coma is as bad as diabetic coma. It is difficult to define unfitness for driving in terms of mental or cerebral disease, because these conditions often occur as temporary states. The important conditions in this respect probably are recognized cerebral or mental disease such as epilepsy, head injuries, alcoholism, etc.

Is Speed Synonymous with Carelessness or Recklessness?

Temporary instability or irresponsibility are examples of abnormal mental conditions that can be defined and considered in relation to road safety. Both of these states, especially the former, are generally curable with time or preventive measures, and licences could be withheld or suspended as a temporary measure. Licences should be permanently withheld from chronically unstable or irresponsible individuals, such as the habitual criminal and the drunkard, subject to special provision for the granting of licences to exceptional cases, e.g. the socially rehabilitated on the recommendation of responsible persons or bodies such as social welfare workers, the clergy, etc. Lastly, the habitual 'speed-merchant', who cannot bear to let another pass him or retain the lead against him, who races to arrive in time for a casual appointment, and who does not see that the extra minute he may save makes no difference, should have his activities curtailed. His love of speed may be due to high spirits and competitiveness, or to a warped mind. From a medical point of view, habitual speeding is a sign of mental instability and should be a reason for the cancellation of a driver's licence.

Speed is one of the most important causes of death on our roads. A person who drives a car at high speed, even on a straight, well-constructed highway, whether he realizes it or not, is forgetting two things: His own fallibility as a human being and the role of external factors such as a dog, a child, a sheep, a bird, a nervous or careless driver, or an unthinking pedestrian. A driver has no control over external circumstances. He can only attempt to control and manipulate his own car, and at high speeds his control and ability to manipulate his car is at its minimum.

Is Third Party Insurance Wholly Good?

Insurance, which is of great psychological significance, was originally intended to ensure compensation to injured parties when the person causing the accident was not able to meet the cost of the damage he caused. In this sense insurance is good, but there is another side to it. Insurance may give the motorist a false sense of security—he may begin to drive 'under the influence' of insurance. He knows that an accident need not lead to financial embarrasment, for his insurance company will foot the bill, and so he gives less thought to the death, destruction and grief which may follow on his carelessness or recklessness. Every man should be held responsible for the harm caused to others through his negligence.

THE CURE

The cure for road accidents does not lie in safety belts, crash helmets, car designs, blood donors, surgical teams, and courtesy weeks. These measures are good, but are a mere drop in the ocean. The solution lies in public health measures. On the surface, town planning, sewerage installation and rodent extermination may appear to be non-medical measures, but they are in fact public health measures governed by public health regulations. Road safety falls into a similar category and I shall now try to show how the existing measures fall short or are out of date.

The Road, the Vehicle and Speed

National roads are designed for a maximum safety speed of 50-60 miles per hour. However, safety does not only depend on the road and the vehicle, but on the human being behind the wheel. The average person cannot stand the strain of high speeds, except over short distances. If he is driving a long distance and is to avoid fatigue and strain, a driver must maintain a moderate rate of travel. A tired person is accident prone and so is a speeder.

In a large car, a good, moderate speed on a national highway would be that advised by the engineers, namely 50-60 miles per hour. In a smaller car, or in an old car the factor of fatigue in the driver will be increased, and for such cars the cruising speed on national highways should be accordingly decreased.

In dealing with country roads, the speed limit for each class of vehicle should be reasonably reduced.

Vehicles should be marked so as to indicate their speed class. Both driver and public would then know if a vehicle was speeding and the police could then intervene. Governors should also be used.

The Driver and the Vehicle

Both driver and vehicle should be examined periodically. The results of these tests should be filed with the Issuer of Licences. Naturally, if a driver or vehicle should fail to qualify, he or it will have to go off the roads until such time as they do qualify.

A person with a physical defect, who, for example, has lost the use of, or partial use of, a limb or limbs, should undergo a special test and be permitted to drive only a specially adapted car. A special speed limit should be fixed for such drivers and their cars should carry a distinctive outward mark.

The Examiners and the Police

Both civil and traffic police should know the traffic laws, even if they do not hold drivers' licences, and should be urged to report the behaviour of motorists, if they contravene the laws. In smaller towns, where there are no traffic police, the civil police often tend to become casual about traffic offences, whereas they should be more alert than the officials in larger towns.

Both examiners for driving licences and traffic policemen should pass a special driving test, and they should be subject to periodical examination. There should be two kinds of traffic policemen; mounted and pedestrian. In each case they should operate in pairs as far as possible. This would ensure that their evidence would be accepted in a court of law.

In urban areas, where the traffic is heavy, each pair of pedestrian policemen should walk their beat abreast in the same direction, but on opposite sides of a street. In this way they would both be liable to see the same incidents and could compare notes afterwards.

On highways, the traffic police should, of course, be mounted on fast vehicles but, until an incident calls for investigation, their travelling speed should be such that they are able to notice what is going on about them, just as a London policeman is bound to pace his beat at 2 miles per hour. These policemen should also operate in pairs.

In addition to the police there should be civilian road-safety officers, consisting of men of good character appointed for their interest in road safety. They should carry a badge of office and should have at least some of the powers of traffic police. Especially in the smaller towns where there are no traffic police, a small unit of civilian officers would be of great help.

Alcoholism and Other Diseases

Alcoholism and other diseases affecting driving ability should be made notifiable. With regard to the present offence of driving under the influence of alcohol or narcotics, many people evade their real liability because the doctors are sometimes unable to state what their condition was at the time they were alleged to be driving the car. The definition of the offence should be changed so that any person who has taken alcohol or narcotics in such quantity as to affect his driving ability at any time thereafter (whether soon or after a lapse of time) should not be permitted to drive a car at all.

Penalties

The subject of penalties is difficult and to a large extent must be left in the hands of judges and magistrates. I should, however, like to make the following suggestions:

(*a*) Drivers who are continually appearing in court for offences relating to nuisances, speeding, carelessness, etc. should ultimately be declared habitually unfit for driving.

(*b*) A driver who is involved in an accident caused by his own recklessness, alcoholism or indifference to traffic rules, should have his licence cancelled with permission to re-apply after a period fixed by the court.

(*c*) A driver who is found guilty of driving under the influence of alcohol or narcotics, or who is found guilty of driving a car after having taken alcohol or narcotics in such quantity as to affect his ability to drive, should be penalized as indicated in (*b*) above.

A driver who is twice found guilty of either of the abovementioned offences should be declared habitually unfit for driving.

(*d*) A person who has been declared habitually unfit may be allowed to re-apply for a driver's licence after a stipulated period.

(*e*) The temporary cancellation of a licence with the right to re-apply at some future time will only be effective if my suggestions for the testing of applicants with regard to character, health and driving ability, are adopted.

We must, of course, try to retain a sense of proportion and humour, but if measures of the nature suggested in this article were adopted, the results might be profound.

OPKNAPPINGSKURSUS NAGRAADSE SKOOL : POSTGRADUATE SCHOOL REFRESHER COURSE

Die Nagraadse Skool-beplanningskomitee het 'n opknappingskursus wat sal handel oor interne geneeskunde, in die Doktersteekamer, Nasionale Hospitaal, Bloemfontein, vanaf 26—28 November 1959, beplan. Diegene wat belangstel word versoek om die Ere-Sekretaris, Posbus 834, Bloemfontein, vóór 21 November in kennis te stel.

The Postgraduate School Steering Committee has organized a medical refresher course to be held in the Doctors' Tearoom, National Hospital, Bloemfontein, on 26—28 November 1959. Those who are interested are asked to inform the Hon. Secretary before 21 November.

PROGRAM : PROGRAMME

Donderdag/Thursday 26 November		
2.00— 3.00 nm./p.m.	Galblaassiektes	Dr. D. J. J. Bezuidenhout.
3.30— 4.30 nm./p.m.	Dysphagia	Dr. W. Grundill.
8.00—10.00 nm./p.m.	Kliniese aand/Clinical evening	Dr. F. P. Scott.
Vrydag/Friday 27 November		
8.30— 9.30 vm./a.m.	Allergie by kinders	Dr. C. V. du Toit.
10.00—11.30 vm./a.m.	Splenography and portal hypertension	Dr. S. S. A. Brett.
12.00— 1.00 nm./p.m.	Hartklanke	Dr. J. D. Meyer.
2.00— 3.00 nm./p.m.	Enigma van mangels	Dr. P. M. S. Fischer.
3.30— 4.30 nm./p.m.	Rheumatic disease	Dr. I. Sacks.
4.30— 5.30 nm./p.m.	Die gebruik van digitalis	Dr. G. W. Snyman.
Saterdag/Saturday 28 November		
8.00— 9.00 vm./a.m.	Heart disease in pregnancy	Dr. N. Sacks.
9.30—10.30 vm./a.m.	Depressions	Dr. P. H. L. Barker.
10.30—11.30 vm./a.m.	Elektroliete	Dr. von Wezel.

IN DIE VERBYGAAN : PASSING EVENTS

Dr. C. W. Coplans, of Cape Town, has recently returned from a trip to England and the USA, where he visited physical medicine centres. In New York he lectured at the Bellevue Medical Centre and at the Institute of Physical Medicine and Rehabilitation, New York University.

* * *

Dr. L. M. Marchand, Associate Secretary of the Medical Association of South Africa, transferred his office to Pretoria at the beginning of this month. All correspondence dealing with medical aid societies should be addressed to Dr. Marchand at P.O. Box 1521, Pretoria.

Dr. L. M. Marchand, Medesekretaris van die Mediese Vereniging van Suid-Afrika, het sy kantoor na Pretoria verplaas aan die begin van hierdie maand. Alle briefwisseling in verband met mediese hulpverenigings moet aan dr. Marchand geadreseer word; Posbus 1521, Pretoria.

* * *

Dr. I. N. (Solly) Marks, formerly medical registrar to the Gastro-intestinal Unit, Western General Hospital, Edinburgh, and instructor in medicine and research associate in gastro-enterology at the Temple University Hospital, Philadelphia, USA, has commenced practice as a specialist physician at 302 Medical Centre, Heerengracht, Cape Town. Telephone: Rooms 2-0277.

Dr. I. N. (Solly) Marks, voorheen geneeskundige registrateur aan die Gastro-intestinale Eenheid, Western General-Hospitaal, Edinburgh, en dosent in medisyne en mede-navorser in gastro-enterologie aan die Temple Universiteitshospitaal, Philadelphia, V.S.A., het begin praktiseer as spesialis-internis te Mediese Sentrum 302, Heerengracht, Kaapstad. Telefoon: Spreekkamer 2-0277.

* * *

The British College of General Practitioners. A Symposium on *Prescribing and Therapeutic Trials in General Practice*, sponsored by the Wellcome Foundation, will take place in London on Sunday 22 November 1959. The morning session, under the Chairmanship of the President of the College, will be on 'The use of drugs in general practice' and the afternoon session, under the chairmanship of The Rt. Hon. Lord Cohen of Birkenhead, M.D., D.Sc., LL.D., F.R.C.P., will be on 'Therapeutic trials in general practice'.

* * *

The Atlas Assurance Co. Ltd. have announced that their Malpraxis Policy has been widened and that the present restrictive limits of liability for legal costs incurred in the defence of a criminal charge, a hearing before the South African Medical and Dental Council, or an appeal against a decision of the Medical Council, have been abolished. In addition, provision for legal representation at an inquest has been included in the policy, also without limit of liability. Premium charges will remain unchanged. All policy-holders of the Atlas Assurance Company will receive full particulars when their policies fall due for renewal. In the meantime the extended cover will be held to apply to all cases which arise after the date of this announcement.

* * *

Bristol Floating Trophy. Bristol Laboratories International have presented a silver trophy to the Medical Association of South Africa for a bowls competition to be held during the Association's biennial Congresses. The Floating Trophy was presented for the first time at the 42nd South African Medical Congress held in East London last month. The competition for the trophy is in the form of a 'mixed rinks' for doctors and their wives who attend Congress. This year the trophy was won by Mmes. F. Drusinsky and W. Waddell and Drs. O. M. Haarburger and A. Z. Butt ('skip'), who each received a miniature cup to mark the occasion. The Trophy was presented at the braaivleis given to Congress delegates by the Mayor of East London after the sports afternoon on 1 October.

* * *

Wellcome Trust Grants. Two South African doctors are included in the 1959 'Honours List' of the Wellcome Trust. Grants totalling over £400,000 for the advancement, throughout the world, of research in human and veterinary medicine and allied sciences were made by the Trust during the 12 month period ended 31 August 1959. Of this amount £42,500 was provided for research assistance or expenses. Two of the beneficiaries from this allocation are Dr. G. S. Getz, of the Department of Pathology, University of the Witwatersrand, and Dr. W. P. U. Jackson, of the Department of Medicine, University of Cape Town. Another grant awarded in Africa was one up to £12,500 to provide a mobile laboratory and an animal house for the Makerere College of the University of East Africa.

* * *

The Lilly Educational Fellowship Programme, through which the Eli Lilly International Corporation sponsors physicians from all areas of the free world who wish to visit the USA to further their medical studies, was established shortly after World War II. The aim of the fellowship programme is to promote a better understanding and to establish closer ties between members of the medical profession in the USA and in other countries, and to contribute to postgraduate medical education. Physicians selected to participate in the fellowship programme are chosen by fellow members of the medical profession in their home countries. While in the USA they study in medical colleges or institutions of their own selection. Their studies may be in general medicine and its related fields or any of the medical specialities. 110 fellowships have been granted to physicians from other countries under the fellowship programme since 1945. Before the fellows return home they are shown around Lilly research and manufacturing facilities in Indianapolis and other centres. In 1959 the Lilly International Fellow from South Africa was Dr. E. B. D. Dowdle, of Cape Town.

* * *

Scottish University Graduates' Reunion. An innovation at this year's Medical Congress was the Scottish University Graduates' Reunion held at the Carlton Hotel, East London, on 2 October, which has been acclaimed by all present as a most successful gathering. The function was honoured by the presence of the President of Congress, Dr. P. F. H. Wagner, and by several overseas guests attending Congress.

Initiated by a grand march to the skirl of the bagpipes, and by an address of welcome by Dr. Hamilton Dyke, Chairman of the local 'Reunion' Committee, the evening, with its messages of greeting from principals of the 4 Scottish universities, moved to a climax made possible by the kindly cooperation of the Chief (Dr. Swanson Gray) and members of the local Caledonian Society and by the Stella Logan School of Dancing. This took the form of an exhibition of Scottish country dancing and of Highland dancing, excellent in its presentation and immensely appreciated by Scots and other guests alike. Added to that was the pawky humour and clever story telling and mimicry of the octogenarian, Dr. Whiteside Robertson, to whom special tribute was paid by Dr. J. McCabe, President of the Border Branch. The whole Scottish flavour of the gathering was much enhanced by the broad Scots of Mrs. Swanson Gray's recitation, by the tartan of kilts and kirtles and by the colourful reproduction of the Scottish university crests in an artistic setting of St. Andrews and Scottish standards which adorned the walls.

Proceeds from the function amounting to £17 17s. 0d. have been donated to the Benevolent Fund of the Medical Association. In speeches at the gathering the suggestion was put forward that similar 'reunions' should become a feature of future Congresses, and it is further suggested that different university or medical school groups (e.g. South African, London, etc.), might sponsor such functions.

NUWE PREPARATE EN TOESTELLE : NEW PREPARATIONS AND APPLIANCES

BRISTACIN

B.L. Pharmaceuticals (Pty.) Ltd., introduce Bristacin, a new antibiotic, and supply the following information:

The insolubility of tetracycline base, tetracycline hydrochloride and tetracycline phosphate complex at physiologic pH ranges has limited their use intramuscularly and intravenously.

Bristol Laboratories have succeeded in changing the basic molecular structure of tetracycline, resulting in a clinically more useful form of the antibiotic. A pyrrolidinomethyl group has replaced one of the hydrogen atoms in the NH_2 group, resulting in a much more soluble compound than tetracycline, and hence better adapted to clinical use.

Bristacin and tetracycline hydrochloride have the same spectrum, so that the same organisms are sensitive or resistant to both.

When Bristacin in 350 mg. doses is administered every 24 hours, serum levels reach a peak within approximately 1 hour, and decline to a minimum or trough level at 24 hours. If Bristacin is given in 350 mg. doses every 4 hours, the peak levels are, in general, no higher than on a 24-hour schedule, but of course they occur twice as often. The principal advantage of the 12-hour schedule in severe infections is that the trough levels at 12-hour intervals are much higher.

Bristacin in 150 mg. single doses produces tetracycline serum levels approximately as high as those following a single intramuscular injection of tetracycline (250 mg.).

Reports from a number of investigators have shown successful results with Bristacin in a variety of infections. Microorganisms that were successfully eliminated included *Escherichia coli*, *Proteus mirabilis* and *vulgaris*, *Aerobacter aerogenes*, *Klebsiella pneumoniae*, *Streptococcus faecalis*, *Staphylococcus aureus*, alpha streptococci, meningococci and *Brucella suis*. The disease states treated with Bristacin include pyelonephritis, cystitis, epididymitis, cholecystitis, soft tissue infections, brucellosis, mediastinitis, empyema, and osteomyelitis.

Bristacin is available in a complete range of parenteral preparations making it extremely convenient for the doctor to adjust his dosage or mode of parenteral administration.

Bristacin is supplied in vials of 150 mg. and 350 mg. with a 2·0 c.c. vial of sterile water for intramuscular use, and in vials of 700 mg. with a 10·0 c.c. vial of sterile water for intravenous use.

Medical literature may be obtained from B.L. Pharmaceuticals (Pty.) Ltd., P.O. Box 2515, Johannesburg.

BOEKBESPREKINGS : BOOK REVIEWS

SANITATION

The Practice of Sanitation. 3rd edition. By Edward Scott Hopkins and Wilmer Henry Schulze. Baltimore: The Williams and Wilkins Company. 1958.

Please note that Messrs. Ballière, Tindall and Cox Ltd., of London, are the English distributors of this book, which was reviewed in the *Journal* of 29 August (**33,** 736). The English price is 64s.

APPLIED PHARMACOLOGY

Applied Pharmacology (*Clark*). 9th edition. By A. Wilson, M.D., Ph.D., F.R.F.P.S. and H. O. Schild, M.D., Ph.D., D.Sc. Pp. xii + 750. 165 figures. 50s. net. London: J. & A. Churchill Ltd. 1959.

The first edition of this well-known book by a famous pharmacologist was published in 1923, not long after the author had left the University of Cape Town where he had been for a short time the first incumbent of the Chair of Pharmacology. In the recent editions the new authors have preserved the original characteristic features of the book—the presentation of direct scientific evidence for the therapeutic action of the more important drugs and the demonstration of the importance of this knowledge in their clinical application. The student—undergraduate and post-graduate—is provided with a background of factual knowledge and learns a critical approach to the increasingly complex problems of drug therapy. Most of the chapters have been rewritten, and new chapters added on the pharmacology of tuberculosis and on psycho-pharmacology. The methods of studying the action of drugs on the central nervous system are described, based on their effects on the gross behaviour and on the psychological reactions in animals and man. There are also 65 new figures and 50 more pages. 'Good wine needs no bush.' N.S.

AUSCULTATION AND PERCUSSION

Lehrbuch der Auskultation und Perkussion. 2. Auflage. Von Prof. Dr. K. Holldack. xii + 196 Seiten. 85 Abbildungen. DM 16.50. Stuttgart: Georg Thieme Verlag. 1959.

Right from the onset it may be said that this book affords pleasant reading irrespective of the status of the reader concerned. It is primarily compiled and intended for the training of medical students and as such covers the field very adequately. Special emphasis is laid on technique of percussion and special site of auscultation together with interpretation of the essential heart sounds, inclusive of systolic click and opening snap heard in pulmonary hypertension and mitral stenosis respectively. Equally important emphasis is laid on the use of the stethoscope in the examination of the abdomen and peripheral vascular system.

The contents of this book are of such imperative nature that any teaching institution can ill afford to exclude it from its library. The book is strongly recommended by the reviewer; money spent on buying it will be money intelligently invested. D.J.H.

RADIOGRAPHY OF THE INFANT'S ALIMENTARY TRACT

X-ray Diagnosis of the Alimentary Tract in Infants and Children. By Edward B. Singleton, M.D. Pp. 352. 215 figures. $11.00. Chicago: Year Book Publishers, Inc. 1959.

This book provides a long-needed addition to radiological literature. In the post-war years there has been dramatic advancement in the surgery of the alimentary tract of infants and children, which has been largely aided by radiological methods and techniques that ensure more accurate pre-operative diagnosis. The author in particular pays much attention to such radiological manœuvres and methods, which he describes in detail. Congenital abnormalities are dealt with at great length, and their embryology and pathology are discussed in addition to their radiological appearances and methods of treatment.

The oesophagus is fully described, in particular the subjects of partial thoracic stomach and atresia.

Of special interest is the vexed question of the reduction of intussusception in infants. The author favours treatment by barium enema with operation as a second string to his bow. These methods are apparently the choice at his hospital in Texas, USA, as well as at many large centres of Scandinavia and Australia.

This book is well illustrated and printed on excellent paper, and is thoroughly recommended to radiologists, paediatricians and paediatric surgeons. I.O.F.

CHRIST AND FREUD

Christ and Freud. A Study of Religious Experience and Observance. By Arthur Guirdham, M.A., D.M., B.Sc. (Oxon), D.P.M. Pp. 193. 21s. net. London: George Allen & Unwin Ltd. 1959.

Dr. Guirdham's aim is to study the psychiatric foundations of religion and, conversely, to estimate to what extent religious factors are important in relation to psychiatric conditions and more especially to neurosis. He believes that orthodox Christianity is a perversion of the psychologically irrefutable teaching of Christ and he shows how theology may actually be inimical to religious experience. A.H.T.

HISTORY OF OPHTHALMOLOGY

A History of Ophthalmology. George E. Arrington, Jr., M.D. Pp. 174. $4.00. New York: MD Publications, Inc. 1959.

This short monograph deals concisely with the ophthalmological chapter of the history of medicine, viz. the study, at first empiric and later scientific, of the vital sense organ which through the centuries has been most closely linked with superstitions, myths and legends. From the early probings of prehistoric man, the development of the scientific method is in turn influenced by the spirit of freedom of expression and criticism of the Greeks, the realism of the Romans, the dogmatism of the Middle Ages; but with the development of printing and easy communication and general progress in associated fields it makes its greatest advances. This tremendous territory is covered succintly but without loss of lucidity or coherency. The considerable collateral historical material adds interest in the discussion of the general tendencies which are stressed, rather than purely biographical aspects. Unfortunately there are numerous typographical errors and the paper is not of the quality associated with American publications, but the book is nevertheless well produced and makes interesting reading. L.S.

BIOCHEMISTRY OF CLINICAL MEDICINE

The Biochemistry of Clinical Medicine. 2nd edition. By W. S. Hoffman, Ph.D., M.D., F.A.C.P. Pp. xxi + 734. 63 figures. $12.00. Chicago: Year Book Publishers, Inc. 1959.

It takes a book such as this to make one realize just how large a part biochemistry plays in modern clinical medicine and how difficult it must be to keep abreast of recent developments. It aims at presenting in a lively and readable manner the fundamental biochemical aspects of clinical medicine . . . and to elucidate that portion of the vast array of recently assimilated information in biochemistry that will help the clinician in the practice of medicine. Dr. Hoffman has admirably fulfilled these laudable aims.

The book is comprehensive in its scope, accurate in its detail, and simple and yet fundamental in its approach; all in all it is a pleasure to read. The author passes with effortless ease from a discussion on carbohydrates to one on lipids, from the kidneys to the liver and other organs and from the thyroid to steroids. He even wanders, perhaps a little less convincingly, into blood coagulation and other aspects of haematology as well as into many other fields. In the chapters where Dr. Hoffman speaks from his own very extensive experience and his own fundamental contributions he speaks with firm authority, even with dogmatism; in other chapters his touch is not quite so sure but, then, who can be complete master of all he surveys? But even these last-mentioned chapters are more than adequate.

Sometimes the approach is purely from a theoretical and laboratory angle; at other times there are complete clinical essays. The author has not hesitated to discuss signs, symptoms and differential diagnosis. Even advice on treatment is freely offered. At the end of each chapter there are short lists of references—not aiming at being exhaustive, yet adequate as a starting point for further reading.

This book will appeal to candidates for higher examinations, to physicians and surgeons, and to those practitioners who wish to revise their knowledge of biochemistry in clinical medicine. It is heartily recommended. C.M.

PARASITOLOGY

Parasitology (Protozoology and Helminthology) in Relation to Clinical Medicine. 2nd edition. By K. D. Chatterjee. M.D. (Calcutta). Pp. 188. 94 illustrations, including 16 coloured plates. Price in India, Rs. 17.50. Calcutta: Published by the author. 1959.

The reviewer was very pleased to see a smaller version of Chatterjee's *Human Parasites and Parasitic Diseases* to which the main objection was its prohibitive price. The present volume is within the reach of students and will form good introduction to the subject. The illustrations are superb, and so are the tables. Though there are points in the text with which the reviewer would differ, the material is sound, and the book can be recommended to student and practitioner alike. R.E-D.

SKIN DISEASES IN THE AFRICAN

Skin Diseases in the African. By G. H. V. Clarke, M.A. (Cantab.), M.B., B.S., A.R.I.C. Pp. ix + 172. 260 figures. 84s. net. London: H. K. Lewis & Co. Ltd. 1959.

Dr. Clarke has made a valuable contribution to dermatological literature in compiling this atlas of dermatoses affecting the negro. The diseases are presented in groups which contrast their incidence on black and white skins, and where a condition is not illustrated the reader is referred to a comprehensive bibliography. The illustrations appear to come almost entirely from the author's collection, and it is admitted that they are of varying quality; most are good, but there are a few rather murky specimens.

It is plain from this book, written from experience in Nigeria, that the incidence of skin diseases in the negro races varies from one part of Africa to another. Porphyria is common in the Bantu of South Africa, but evidently not in Nigeria. Dermatosis papulosa nigra is often seen in East and South Africa, but is very rare in West Africa and there are other differences too numerous to discuss in a review.

There are a few minor criticisms, some anticipated by the author. The lesions of folliculitis decalvans here depicted resemble those of chronic discoid lupus erythematosus so closely as to make the diagnosis doubtful. The condition illustrated under the title of multiple self-healing epitheliomata is not that described by Ferguson Smith and the appearances suggest a chronic granuloma. Behçet's syndrome should not be listed under venereal diseases.

This book will be of great service to any newcomer to Africa, but for future editions the author should not hesitate to borrow in order to illustrate conditions that are common in parts of Africa other than Nigeria, to which he now only makes reference. J.M.

BRIEWERUBRIEK : CORRESPONDENCE

POISONOUS SNAKE BITES

To the Editor: I do not want to draw any conclusions from a single case and I would therefore be interested to know whether any colleague has had experience in the following matter regarding poisonous snake bites.

We have in this area one of the most poisonous snakes in the country, known as the bergadder. It does not hibernate and bites occur all the year round. Both systemic and local reactions are very severe and death is common.

The first case I saw was a European boy of 12 years, who was bitten near the ankle in July 1958. In spite of 20 c.c. of Fitzsimmons antiserum within 1 hour after the bite and repeated injections of calcium gluconate intravenously, his condition deteriorated so rapidly that I had to send him to hospital in Port Elizabeth on the third day. In spite of the very best treatment, including blood transfusions, his life hung in the balance for about 3 weeks and he had to have his leg amputated below the knee owing to incipient gangrene caused mainly by massive and persistent local oedema. He is now quite well.

In August this year I treated a Coloured girl of 16 who had been deeply bitten in the foot near the ankle by a bergadder. I gave her 30 c.c. of antiserum and 20 c.c. of calcium gluconate and I injected 10 c.c. of the antiserum locally around the wound. I also saw her within 1 hour after she was bitten. But, and this is the point, I also gave her 12 varidase buccal tablets with instructions to dissolve 1 underneath the tongue every 4 hours, and to report immediately if her condition deteriorated. The next day she was reported to be worse and, remembering my previous experience, I sent her off to hospital immediately. Again there was excessive local reaction with oedema of a very severe degree. Much to my surprise, however, I received a telephone

call from the hospital on the third day after her admission to say that she was fit for discharge.

What I would like to know is whether I could ascribe the very favourable outcome in the latter case to the use of the varidase tablets and whether they should be used as a routine in all cases of bites from poisonous snakes?

J. G. Botha

'La Mer'
Plettenberg Bay, C.P.
27 October 1959

METHOD OF LOOSENING SYRINGE PLUNGERS

To the Editor: 'Seized up' syringes are a constant source of loss and annoyance. I was able, very simply, to remedy this defect on 3 occasions, by injecting G11 into the barrel and allowing the syringe to stand, so that the plunger was below the column of G11. After 1-3 hours I was able to remove the plungers. Probably, if the syringe were to stand overnight, it would allow more time for the fluid to seep into the crevice between the plunger and the barrel.

The syringes involved were glass barrels with metal plungers, and a glass plunger in one instance.

H. Fine

434 Westwalk
390 Smith Street, Durban
23 October 1959

THE KUX OPERATION

To the Editor: It is clear from Dr. D. Webster's reply[1] to my letter[2] that he is a Kuxist (Afrikaans: koeksister). May I draw his attention to the fact that my *nom de plume* was *R.S.V.* and not meant to be *R.S.V.P.*

R. S. Verster

Cuthberts Building
Maitland Street
Bloemfontein
3 November 1959

1. Correspondence (1959): S. Afr. Med. J., 33, 925 (31 October).
2. *Idem* (1959): *Ibid.*, 33, 467.

MEDICAL AID SCHEMES

To the Editor: Added to the headaches caused by the various medical aid societies and their rules and forms, we now have companies and societies not recognized by the Medical Association, that mislead their members and put doctors in a poor light in the eyes of their patients.

Here is a quotation from a printed note addressed by the Managing Director of the South African National Sickness and Accident Insurance Co. Ltd. (SANSA), to members who receive normal accounts from us:

'The benefits allowed herewith represent 100% of the fees according to the Preferential Tariff dated January 1959, i.e. the specially reduced Tariff at present allowed to members of approved sick funds by doctors and specialists. Since our medical aid scheme provides a valuable service to the medical profession it is reasonable that reduced fees according to the Preferential Tariff should be applied as is already done by many doctors.'

Without informing its members that this company is not recognized by the Medical Association, the Director's remarks leave the impression that it is.

I think that SANSA, far from rendering 'valuable service' to the profession, is doing us harm; that it is not reasonable that reduced fees should be applied to its members and that, if other doctors are indeed charging reduced fees, they should be put wise to it.

Incidentally, I feel that the responsible committees of the Medical Association should take more active steps to wipe unrecognized medical aid societies from the face of our 'medical earth'.

Fifteen bob

Johannesburg
28 October 1959

PARAPLEGIC EMPIRE GAMES

To the Editor: It is the intention of the Paraplegic Association of Western Australia, acting through the Royal Perth Hospital, Perth, Western Australia, to arrange for and conduct a Paraplegic Empire Games just prior to the Empire Games to be held in Perth in 1962.

I should be most grateful if you could make mention of this fact in your *Journal*, inviting any person interested to communicate with me over the matter, for it is hoped that teams will reach Perth from all over the Commonwealth countries.

Further details will be supplied on application, as to who is arranging for the team in each particular country.

I should be most grateful for your assistance in this matter, as my Committee hope that this will be made as widely known as possible.

G. M. Bedbrook
Secretary

Paraplegic Association of Western Australia
Paraplegic Unit
Shenton Park Annexe
Shenton Park
Perth, Western Australia
7 September 1959

NAUDÉ APPEAL FUND

To the Editor: This fund has been open for some 2 years now and although numerous appeals have been published in the *Journal* and personal letters written to various Branches throughout the Union, the response has been most disheartening.

I sincerely hope that the following biblical quotation will be read by all, and notice taken thereof:

> 'Behold, there come seven years of great plenty throughout all the land of Egypt:
>
> And there shall arise after them seven years of famine; and all the plenty shall be forgotten in the land of Egypt; and the famine shall consume the land;'—*Genesis*, ch. 41, vs. 29, 30.

I should like all to bear this quotation in mind when reading the following figures as the position stands with regard to the above fund:

Amount of Bill of Costs	£ s. d.
Attorney/Client costs—Whittle *vs.* Naudé	1,430 17 7
Cost allowed	800 0 0
Balance owing by Dr. Naudé	£630 17 7
Amount Collected to Date	
Between period 30 August 1957–1 February 1958	81 17 6
Between period 21 November 1958–23 July 1959	46 4 6
	£128 2 0

During February 1958 it was decided to hand over to Dr. Naudé a cheque for £100. Although only £81 17s. 6d. had been collected, less the necessary bank charges, etc. the balance was taken from Branch funds. A further appeal was published in the *Journal*, and as can be seen, a sum of £46 4s. 6d. was received.

I should like all members to study the position as put before you, and I am sure you will all appreciate it. Dr. Naudé has suffered a considerable loss, not only financially, but in many other ways, and the least we can do would be to compensate him for the financial loss he has had to bear.

Just remember, any one of you might be in a position such as this, and wouldn't it be most disheartening to know that your colleagues were 'backward in coming forward'.

I appeal once again to you to give the position considerable thought.

J. H. Hofmeyr
Hon. Secretary

Transkei Branch (M.A.S.A.)
P.O. Box 318, Umtata
27 October 1959